

Probabilities of Pulmonary and Cardiac Complications and Radiographic Parameters in Breast Cancer Radiotherapy

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Purpose: To evaluate the relationship between the normal tissue complication probability (NTCP) of 3-dimensional (3-D) radiotherapy and the radiographic parameters of 2-dimensional (2-D) radiotherapy such as central lung distance (CLD) and maximal heart distance (MHD).

Materials and Methods: We analyzed 110 patients who were treated with postoperative radiotherapy for breast cancer. A two-field tangential technique, a three-field technique, and the reverse hockey stick method were used. The radiation dose administered to whole breast or the chest wall was 50.4 Gy, whereas a 45 Gy was administered to the supraclavicular field. The NTCPs of the heart and lung were calculated by the modified Lyman model and the relative seriality model.

Results: For all patients, the NTCPs of radiation-induced pneumonitis and cardiac mortality were 0.5% and 0.7%, respectively. The NTCP of radiation-induced pneumonitis was higher in patients treated with the reverse hockey stick method than in those treated by other two techniques (0.0%, 0.0%, 3.1%, $p < 0.001$). The NTCP of radiation-induced pneumonitis increased with CLD. The NTCP of cardiac mortality increased with MHD ($R^2 = 0.808$).

Conclusion: We found a close correlation between the NTCP of 3-D radiotherapy and 2-D radiographic parameters. Our results are useful to reanalyze the previous 2-D based clinical reports about breast radiation therapy complications as a viewpoint of NTCP.

Key Words: NTCP, Breast cancer radiotherapy, Radiographic parameter, Radiation pneumonitis, Cardiac toxicity

Introduction

Postoperative radiation therapy (RT) can reduce the risk of local recurrence in patients with high-risk breast cancer.^{1~3)} However, RT can lead to pneumonitis or cardiac toxicity. Radiation-induced pneumonitis typically occurs 1 to 6 months after RT; the overall incidence of radiation-induced pneu-

monitis is approximately 1%.^{4,5)} Although radiation-induced pneumonitis is considered to be a trivial issue in most cases of breast RT, it can be problematic in some patients with unfavorable anatomy and an inadequate radiation technique.^{6,7)} Radiation-induced cardiac complications are very uncommon and most studies report no severe effects on morbidity or mortality.⁸⁾ As RT techniques have improved, the risks of radiation-induced pneumonitis and cardiac complication have declined. However, several reports indicate that RT increases the risk of cardiovascular disease and long-term mortality of patients with cancer involving the left breast.^{9,10)} In particular, radiation-induced cardiac mortality can be fatal and may decrease the survival benefit of RT. Thus, it is essential to evaluate the risk of complications during RT planning.

Recently, CT simulators and treatment planning systems have been used to plan RT and to calculate the relevant dose distributions in normal tissues. Using such dose-volume distri-

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bution data, researchers have developed several normal tissue complication probability (NTCP) models to predict the probability of complications in normal tissue. Many NTCP models, such as the Lyman model^{11,12)} and the Relative Seriality model,^{13,14)} have been developed and applied in clinical settings.

Due to the many confounding factors that affect the risk of complications, models that solely use the dose distribution cannot predict the probability of complications in individual patients. In addition, because of the relatively short history of 3-dimensional (3-D) planning, insufficient clinical data are available for predicting the late effects. In contrast, we can use long-term follow-up data to estimate the probability of late complications based on simple radiographic parameters, such as the central lung distance (CLD) and the maximal heart distance (MHD). For the clinical application of an NTCP model in breast cancer RT, we ultimately plan to combine the clinical data of 2-dimensional (2-D) RT and the NTCP values from 3-D modeling. Before studying clinical data, it is essential to evaluate the relationship between the NTCP values and radiographic parameters from 2-D planning.

The purpose of this study was to analyze the relationship between the NTCP values of 3-D RT and radiographic parameters, such as the CLD and MHD of 2-D imaging, using several RT techniques.

Materials and Methods

1. Patients

Between November 2006 and August 2007, 110 breast cancer patients who received postoperative RT were selected for a retrospective analysis. The median patient age was 48 years (range, 27 to 71 years). Fifty-three (48.2%) patients had right-sided breast cancer and 57 (51.8%) patients had left-sided breast cancer.

2. Radiotherapy

RT was performed using the two-field standard tangential technique (n=47), three-field technique (n=47), or reverse hockey stick technique (n=16). All of the patients treated with the two-field technique received breast-conserving surgery. Modified radical mastectomies were performed in patients treated with the three-field technique or reverse hockey stick

technique. The radiation dose to the involved whole breast was 50.4 Gy (1.8 Gy/fraction using 6 MV photon beams in a 2-field standard tangential technique). The boost dose to the tumor bed was 10 Gy (2.5 Gy/fraction using 3-D conformal RT). In the three-field technique, the radiation dose to the involved chest wall was 50.4 Gy (as in the two-field tangential method) with an ipsilateral supraclavicular field at a total dose of 45 Gy (1.8 Gy/fraction). For the reverse hockey stick technique, 6 MV photon and 6 or 9 MeV electron beams were used with a total dose of up to 50.4 Gy (1.8 Gy/fraction). The ipsilateral supraclavicular field was the same as for the three-field method. The CT images, radiation field definitions, and beam setup of these techniques are summarized in Fig. 1.

3. Calculation of the NTCP

We used the GE Light Speed RT (GE Medical Systems, Milwaukee, WI, USA) for CT-simulation and the Eclipse™ planning system (Varian Medical Systems, Palo Alto, CA, USA) for dose calculation. Using the dose calculation data, we derived dose-volume histogram (DVH) curves of each organ-at-risk. From these DVH curves, we performed the NTCP calculations for each NTCP model (Fig. 2). We used the Lyman-Kutcher-Burman model with the data of Emami et al.¹⁵⁾ for radiation-induced pneumonitis and pericarditis. The equivalent uniform dose (EUD) method was used for reducing the DVH curves to a single dose. The Relative Seriality model was used for calculation of the NTCP for late cardiac mortality.^{13,14)} The Lyman-Kutcher-Burman (LKB) NTCP and Relative Seriality models used in this study are briefly described below.^{11~14)}

4. LKB NTCP model

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx$$

$$t = \frac{EUD - TD_{50}}{m \cdot TD_{50}}$$

$$EUD_{LKB} = \left(\sum_i D_i^n \frac{V_i}{V_{tot}} \right)^{\frac{1}{n}}$$

Where TD_{50} is the 50% tolerance dose at 5 years; EUD is

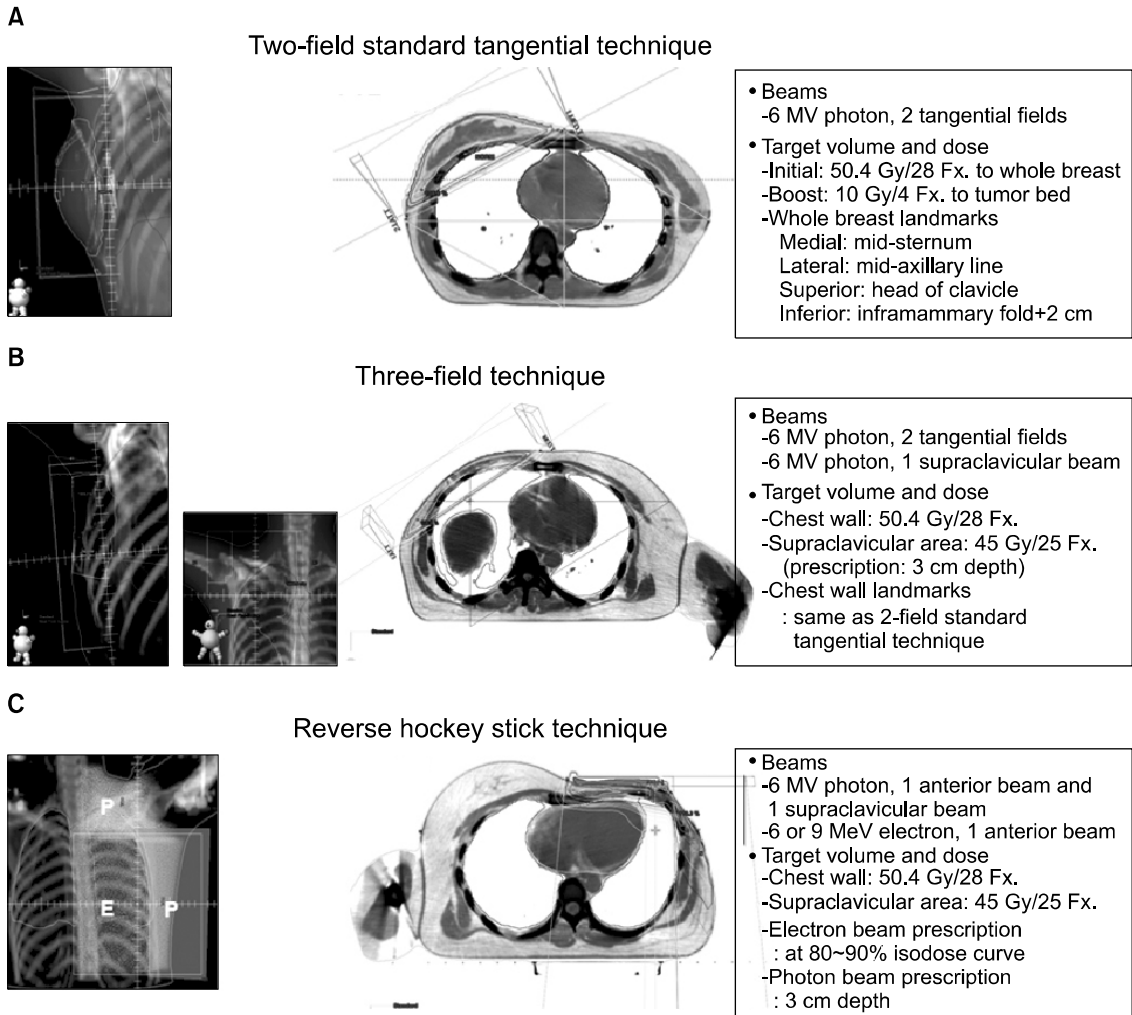


Fig. 1. Field setup and radiation dose prescription in each radiotherapy technique. Two-field standard tangential technique (A), three-field technique (B), reverse hockey stick technique (C).

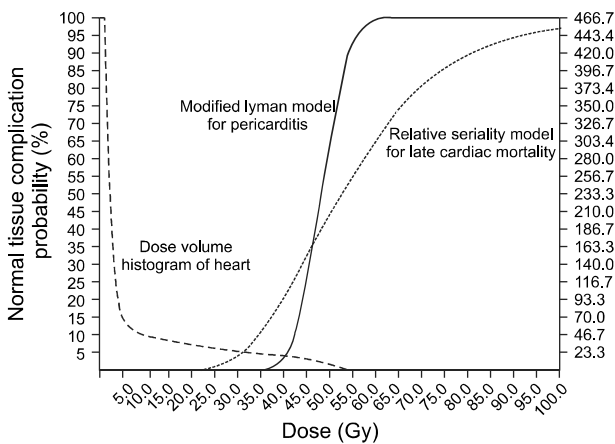


Fig. 2. Dose volume histogram (DVH) of a breast cancer patient and the modified Lyman model and relative seriality model.

the equivalent uniform dose; n and m are tissue-specific parameters; D_i is the dose element; and V_i is the volume element. The parameters for complication of radiation-induced pneumonitis are $TD_{50}=24.5$, $n=0.87$, and $m=0.18$ and the parameters for complication of from radiation-induced pericarditis are $TD_{50}=48.0$, $n=0.35$, and $m=0.10$.

5. Relative seriality model for late cardiac mortality¹⁶⁾

$$NTCP_{\text{heart}} = \left\{ 1 - \prod_{i=1}^n [1 - P(D_i)^s]^{Av_i} \right\}^{1/s}$$

$$P(D_i) = 2^{-\exp\{e\gamma(1-D_i/D_{50})\}}$$

where $D_{50}=TD_{50}$ (=52.3 Gy); s is the relative seriality factor (=1), and γ is the maximum relative slope (=1.28).

6. NTCP according to the CLD and MHD

Twenty left-sided breast cancer patients, using the two-field (n=10) or three-field technique (n=10), were randomly selected from the group of 110 patients. We performed 2 virtual simulations for each patient (2 cm and 3 cm of the CLD). In each plan, we calculated the NTCP of radiation-induced pneumonitis and cardiac toxicity as described above. We evaluated the change in NTCP values of radiation-induced pneumonitis between 2 cm and 3 cm of the CLD. For

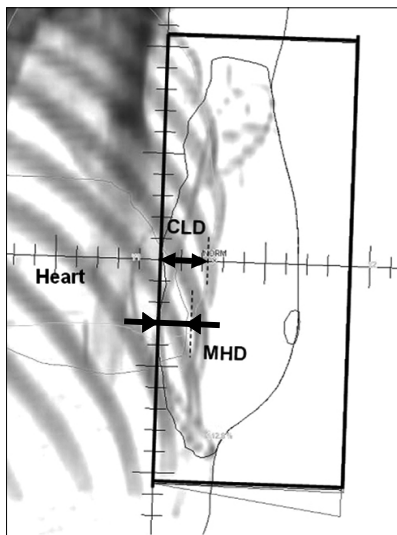


Fig. 3. Central lung distance (CLD) and maximal heart distance (MHD) of a breast cancer patient in virtual simulation.

evaluating the change in NTCP by the MHD, we also measured the MHD in every treatment plan (Fig. 3).

7. Statistical analysis

Statistical analysis was performed using the SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). The one-way ANOVA method or the t-test were used for comparing mean of NTCP, whereas the paired t-test was used for studying the change of NTCP according to the CLD, respectively.

Results

1. NTCP by radiation technique

Considering both lungs as a single organ, the mean NTCP of pneumonitis for all the patients was calculated to be 0.5%. According to the radiation technique, the mean NTCP was 0.0% in the 2- and 3-field radiation techniques and 3.1% in the reverse hockey stick method. Considering the ipsilateral lung as a single organ, the mean NTCPs of radiation-induced pneumonitis were 0.1%, 4.5%, and 6.4% for the 2-field, 3-field, and reverse hockey stick methods, respectively. There was a statistically significant difference in the NTCP between the radiation techniques ($p < 0.001$). By applying the Lyman model, the mean NTCP of pericarditis was 0% for all the radiation techniques. However, when the Relative Seriality model was used to calculate the NTCP of late cardiac mortality, the mean NTCP for all the patients was 0.7%. According to the radiation technique, the mean NTCPs of cardiac mortality were 0.0%, 0.7%, and 1.3% in the 2-field,

Table 1. Normal Tissue Complication Probability (NTCP) of the Lung and Heart by Radiation Therapy

Organ at risk	Total	Radiation technique			p-value
		2-field	3-field	Reverse hockey stick	
Lung (%)	NTCP, pneumonitis (ipsilateral lung)				
	Average	2.9	0.1	4.5	6.4
Range	0~99.1	0~0.3	0.1~26.9	0.9~99.1	
Lung (%)	NTCP, pneumonitis (whole lung)				
	Average	0.5	0.0	0.0	3.1
Range	0~35.2	—	—	0~35.2	
Heart (%)	NTCP, pericarditis (Lyman model)				
	Average	0.0	0.0	0.0	0.0
Range	—	—	—	—	
Heart (%)	NTCP, mortality (relative seriality model)				
	Average	0.7	0.0	0.7	1.3
Range	0~10.5	—	0~3.4	0~10.5	

3-field, and reverse hockey stick methods, respectively (p=0.13) (Table 1).

2. NTCP by laterality

We compared the NTCP of patients with right- and left-sided breast cancer. The mean NTCPs of radiation-induced pneumonitis, considering both lungs as a single organ, were 0.8% for right-sided cancer patients and 0.2% for left-sided cancer patients (p=0.08). The mean NTCPs of the ipsilateral lung were 5.7% for right-sided breast cancer patients and 7.0% for left-sided breast cancer patients (p=0.97). The NTCPs of pericarditis was 0% for all of the patients, regardless of laterality. The NTCP of cardiac mortality in left-sided breast cancer patients was 1.4%, which is significantly higher than the value for right-sided breast cancer patients (0.0%, p<0.001) (Table 2).

3. NTCP of radiation-induced pneumonitis by the central lung distance

There was no significant difference in the NTCP of

radiation-induced pneumonitis by changing the CLD when considering both lungs as a single organ. The NTCP values were close to 0.0% for the 2 cm and 3 cm CLD. However, the NTCP in the ipsilateral lung revealed a significant difference as the CLD increased from 2 cm to 3 cm (3.7% vs. 14.5%, p<0.001) (Table 3). Upon changing the CLD, there were negligible changes in the NTCP of patients treated by the 2-field method; however, there was a significant increase in the NTCP in the 3-field method (Fig. 4).

4. NTCP of cardiac mortality by the maximal heart distance

Fig. 5 shows a correlation between the NTCP values and MHD ($R^2=0.808$). By applying a polynomial fitting, an equation between the NTCP and MHD was derived. Using this graph and equation, we predicted the NTCP of cardiac mortality based on the MHD at the time of simulation. For example, if the MHD is 1.6 cm, the NTCP of cardiac mortality is approximately 2%; if the MHD is 1.3 cm, the NTCP of cardiac mortality is approximately 1%.

Table 2. Normal Tissue Complication Probability (NTCP) of the Lung and Heart in Right and Left-sided Breast Cancers

Organ at risk		Right-sided (n=53)	Left-sided (n=57)	p-value
Lung (%)	NTCP, pneumonitis (ipsilateral lung)			
	Average	5.7	7.0	0.97
	Range	0~99.2	0~96.5	
Heart (%)	NTCP, pneumonitis (whole lung)			
	Average	0.8	0.2	0.08
	Range	0~35	0~4.8	
Heart (%)	NTCP, pericarditis (Lyman model)			
	Average	0.0	0.0	—
	Range	—	—	
Heart (%)	NTCP, mortality (relative seriality model)			
	Average	0.0	1.4	<0.001
	Range	0~1.9	0~10.5	

Table 3. Normal Tissue Complication Probability (NTCP) of the Lung by Central Lung Distance (CLD) in Left-sided Breast Cancers (n=20)

Organ at risk		Central lung distance		p-value
		2 cm	3 cm	
Lung (%)	NTCP, pneumonitis (ipsilateral lung)			
	Average	3.7	14.5	<0.001
	Range	0~26.9	0.2~66.9	
Lung (%)	NTCP, pneumonitis (whole lung)			
	Average	<0.1	0.1	0.07
	Range	0~2.4	0~1.2	

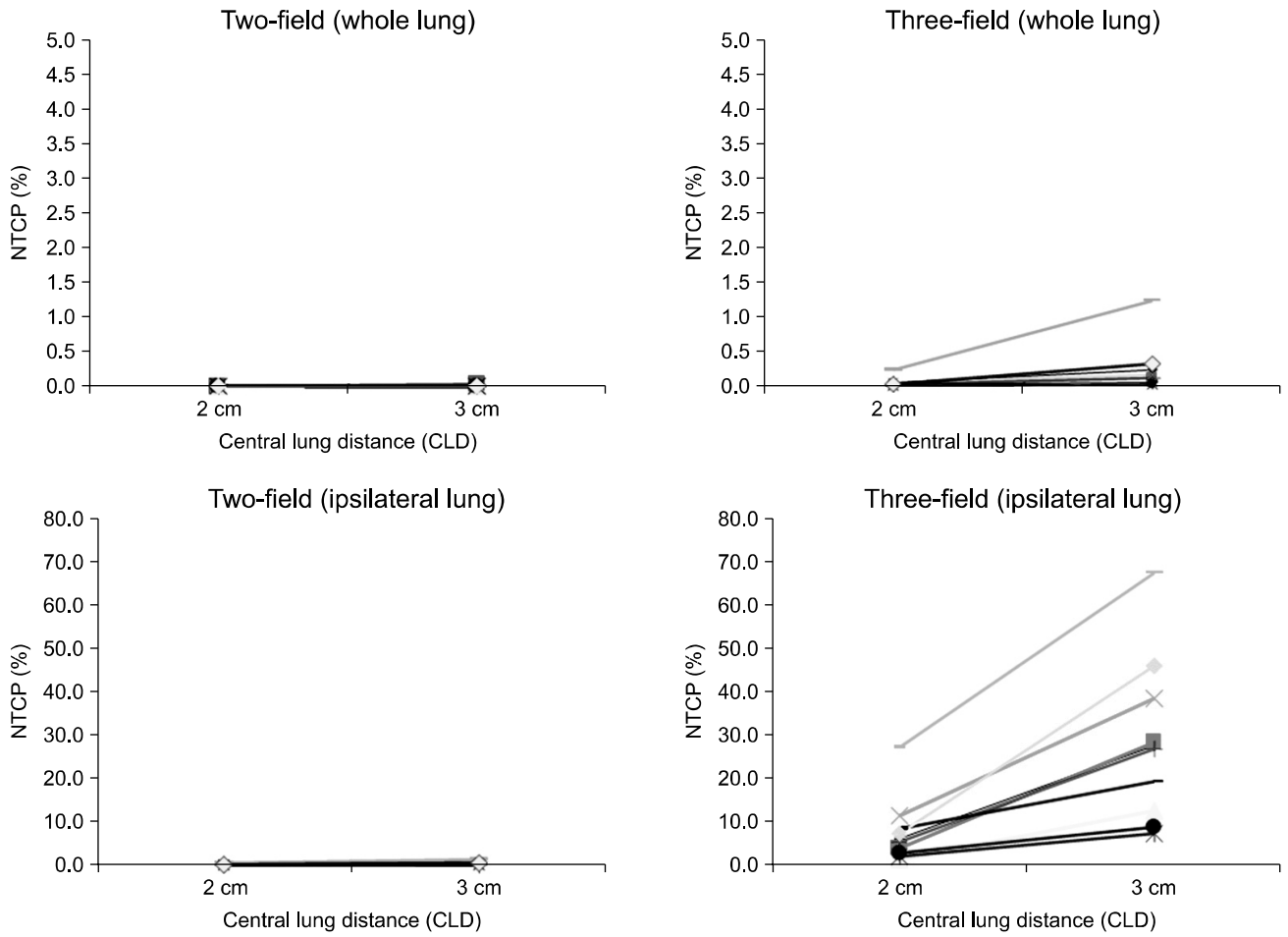


Fig. 4. Normal tissue complication probability (NTCP) change by central lung distance.

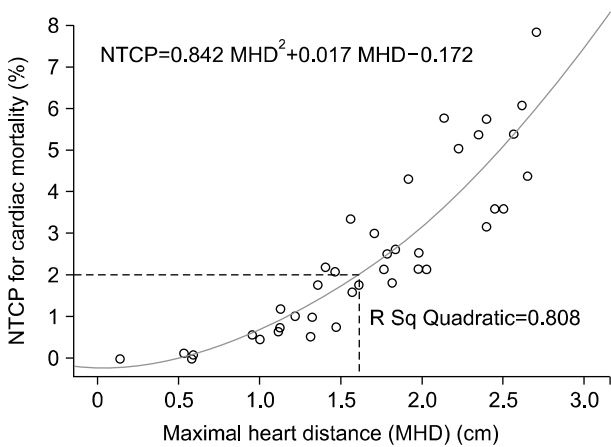


Fig. 5. Normal tissue complication probability (NTCP) of cardiac mortality by maximal heart distance.

Discussion and Conclusion

1. NTCP of radiation-induced pneumonitis and RT technique

Several studies have reported that the incidence of radiation-induced pneumonitis is 1~2%,^{4,5,17,18)} which is similar to our NTCP results (0.5% for all of the patients). Our results showed that the NTCP varies according to the radiation technique. Specifically, the reverse hockey stick method had a higher NTCP than the 2- or 3-field methods (Table 1). It is thought that this effect is due to the presence of the anterior electron field, which elevates radiation dose in lung parenchyma that lies beneath the chest wall. Pierce et al.¹⁹⁾ compared the NTCP of radiation-induced pneumonitis according to radiation technique; the calculated the NTCP for the reverse hockey stick method was 4.98%, which was higher

than the value for the standard 2-field method (0.37%). However, in this study, the reverse hockey stick method treatment was done by 2-D simulation and the lung dose was evaluated not for the treatment but for this investigation. So, the high NTCP values of the reverse hockey stick method in this study, may be biased by the inappropriate dose prescription of 2-D RT.

When we compared the NTCPs of the 2- and 3-field techniques, we found that the NTCP was higher in the 3-field technique. Lingos et al.¹⁸⁾ reported a higher incidence rate of radiation-induced pneumonitis in a technique that used a supraclavicular field and Das et al.⁴⁾ showed that the incidence rates of radiation-induced pneumonitis in the 2- and 3-field methods were 0.1% and 1.5%, respectively. These results are consistent with our NTCP calculations, suggesting that the LKB NTCP model with a reference parameter set²⁰⁾ may be useful for predicting radiation-induced pneumonitis.

2. NTCP of radiation-induced pneumonitis and the central lung distance

It is well known that the volume of an irradiated lung is the most important risk factor for radiation-induced pneumonitis.^{21,22)} The CLD has been used as a simple parameter to assess irradiated lung volume (Fig. 3). In the NTCP model, an increase of the CLD from 2 cm to 3 cm resulted in an overall increase in the NTCP, especially for the ipsilateral lung (Fig. 4 and Table 3). The increase was significant for the 3-field method, but minimal in the 2-field method. These results suggest that the probability of pneumonitis in the 3-field method is more dependent on the CLD, presumably because the supraclavicular field in the 3-field method increases the irradiated lung volume. Therefore, radiation-induced pneumonitis is less likely when the CLD is kept as small as possible. However, the difference of these NTCPs may be insignificant in clinical settings because radiation-induced pneumonitis in the lung apex is typically asymptomatic.

3. NTCP of cardiac complication

Pericarditis is the most common complication caused by RT, but is rarely caused by RT for breast cancer. This is because the heart has a relatively high tolerance and the irradiated volume is very low in breast RT.¹⁵⁾

However, radiation-induced cardiac mortality can occur in

breast cancer RT and this can offset the advantages of adjuvant RT. There has been much debate about whether RT for breast cancer increases the risk of cardiac events, such as myocardial infarction.^{1,2,8,10,23~25)} In our study, the mean NTCP of cardiac mortality ranged from 0~1.3% and there was no difference regarding the applied radiation technique (Table 1). The NTCP of mortality for left-sided RT was significantly higher than right-sided RT (Table 2). This is similar to the results of Paszat et al.,¹⁰⁾ who reported a significantly higher incidence of myocardial infarction following left-sided RT (right vs. left, 1% vs. 2%, $p=0.02$).

4. NTCP of cardiac mortality by the maximal heart distance

Cardiovascular disease-induced mortality caused by RT is correlated with the dose of radiation to the heart and the irradiated volume of the heart.²³⁾ Thus, RT of the left breast may be associated with a higher risk of fatal cardiovascular death.¹⁰⁾ However, several studies have failed to show a difference in the incidence of cardiovascular death following right- and left-sided RT.^{8,25,26)} Our results indicate a higher, but not statistically significant NTCP of cardiac mortality for left-sided tumors. Presumably, this is because modern RT techniques result in less irradiated volume of the heart. Moreover, previous studies did not consider anatomic variations in heart location, a potentially important factor. Even in left-sided breast cancer, some patients cannot be irradiated to their hearts.

The MHD is a simple radiographic parameter that provides a measure of the irradiated heart volume for each patient. Hurkmans et al.²⁷⁾ predicted the NTCP of cardiac mortality using the Relative Seriality model, and suggested a cardiac mortality curve and an equation based on the MHD. We also performed a planning study from 20 left-sided breast cancer patients by adjusting the MHD. When we plotted the NTCP curve and fitted an equation, these were similar to that of Hurkmans et al.²⁷⁾ (Fig. 5). On this curve, the NTCPs of cardiac mortality of 1% and 2% are predicted at the MHDs of 1.2 cm and 1.6 cm, respectively. However, this plot is limited in that it does not consider many other risk factors of cardiovascular disease, such as a history of hypertension, smoking, and use of combined cardiotoxic chemotherapy. Nevertheless, our method for estimating the NTCP from the

MHD may help to reanalyze the previous clinical reports about cardiac mortality. If we re-evaluate the cardiac events and the MHD of the individual patients in the 2-D based clinical reports, we would better understand the adverse cardiac effects of breast RT.

In conclusion, we found a close correlation between the calculated NTCP of 3-D RT and 2-D parameters (CLD and MHD). Because we did not analyze the actual clinical data of complications, it is difficult to apply our results directly to the clinic. However, our main purpose of this study was to use the relationship between the NTCP and radiographic parameters to reanalyze old studies without full 3-D dose distributions. Therefore, our results are useful to reanalyze the previous 2-D-based clinical reports about breast RT complications as a viewpoint of the NTCP.

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국문초록

유방암의 방사선치료에서 방사선학적 지표에 따른 폐 및 심장의 부작용 확률

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노오규 · 박성호 · 안승도 · 최은경 · 이상욱 · 송시열 · 윤상민 · 김종훈

목적: 정상 장기의 부작용 확률(normal tissue complication probability, NTCP) 모델을 이용하여, 중심폐거리(central lung distance, CLD)와 최대심장거리(maximal heart distance)와 같은 이차원 방사선치료의 방사선학적 지표들과 삼차원 입체조형방사선치료의 부작용확률 사이의 관계를 평가해 보고자 하였다.

대상 및 방법: 2006년 11월부터 2007년 8월까지 서울아산병원에서 유방암으로 진단받고 수술 후 방사선치료를 시행 받은 110명을 무작위로 추출하여 분석하였다. 방사선치료는 2문 빔면 조사법, 3문 조사법, Reverse Hockey Stick법을 사용하였고, 유방 및 흉벽에는 5,040 cGy/28회, 쇄골 상부에는 4,500 cGy/25회로 조사하였고, 유방보존술을 시행한 경우에는 원발 병소에 1,000 cGy/4회의 추가치료를 하였다. 모든 환자에서 전산화단층촬영모의치료를 시행하였고, Eclipse Planning System을 사용하여 선량 계산을 시행 후 폐와 심장의 선량 부피 곡선(dose volume histogram, DVH)을 추출하였다. 추출된 DVH를 사용하여 modified Lyman model과 relative seriality model을 통해 NTCP를 계산하고 분석하였다.

결과: 전체 환자의 방사선 폐렴과 심장 사망의 NTCP 값은 각각 0.5%, 0.7%로 낮은 수치를 보였다. 방사선 폐렴의 NTCP는 2문 조사법과 3문 조사법에 비해 Reverse Hockey Stick 법에서 높았다(0%, 0%, 3.1%, $p < 0.001$). 방사선 폐렴의 NTCP 값은 중심폐거리가 커질수록 증가하였고, 심장 사망의 NTCP는 최대심장거리가 커질수록 증가하였다($R^2=0.808$).

결론: 이차원 방사선치료의 방사선학적 지표들과 삼차원 입체조형방사선치료의 NTCP 값 사이에는 밀접한 관계가 있다. 이러한 연관성을 통해 과거의 부작용확률에 대한 자료들을 이차원 방사선치료의 방사선학적 지표들을 이용하여 NTCP 모델의 관점에서 재분석하는데 유용할 것으로 생각된다.

핵심어: 부작용확률, 유방암, 방사선치료, 방사선학적 지표, 방사선 폐렴, 심장 독성