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Radiation-induced Pulmonary Toxicity following Adjuvant Radiotherapy for Breast Cancer

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Purpose: To evaluate the incidences and potential predictive factors for symptomatic radiation pneumonitis (SRP) and radiographic pulmonary toxicity (RPT) following adjuvant radiotherapy (RT) for patients with breast cancer. A particular focus was made to correlate RPT with the dose volume histogram (DVH) parameters based on three-dimensional RT planning (3D-RTP) data.

Materials and Methods: From September 2003 through February 2006, 171 patients with breast cancer were treated with adjuvant RT following breast surgery. A radiation dose of 50.4 Gy was delivered with tangential photon fields on the whole breast or chest wall. A single anterior oblique photon field for supraclavicular (SCL) nodes was added if indicated. Serial follow-up chest radiographs were reviewed by a chest radiologist. Radiation Therapy Oncology Group (RTOG) toxicity criteria were used for grading SRP and a modified World Health Organization (WHO) grading system was used to evaluate RPT. The overall percentage of the ipsilateral lung volume that received ≥15 Gy (V_{15}), 20 Gy (V_{20}), and 30 Gy (V_{30}) and the mean lung dose (MLD) were calculated. We divided the ipsilateral lung into two territories, and defined separate DVH parameters, *i.e.*, $V_{15\ TNGT}$, $V_{20\ TNGT}$, $V_{30\ TNGT}$, MLD_{TNGT}, and $V_{15\ SCL}$, $V_{20\ SCL}$, V_{30SCL}, MLD_{SCL} to assess the relationship between these parameters and RPT.

Results: Four patients (2.1%) developed SRP (three with grade 3 and one with grade 2, respectively). There was no significant association of SRP with clinical parameters such as, age, pre-existing lung disease, smoking, chemotherapy, hormonal therapy and regional RT. When 137 patients treated with 3D-RTP were evaluated, 13.9% developed RPT in the tangent (TNGT) territory and 49.2% of 59 patients with regional RT developed RPT in the SCL territory. Regional RT ($p<0.001$) and age ($p=0.039$) was significantly correlated with RPT. All DVH parameters except for $V_{15\ TNGT}$ showed a significant correlation with RPT ($p<0.05$). MLD_{TNGT} was a better predictor for RPT for the TNGT territory than $V_{15\ SCL}$ for the SCL territory.

Conclusion: The incidence of SRP was acceptable with the RT technique that was used. Age and regional RT were significant factors to predict RPT. The DVH parameter was good predictor for RPT for the SCL territory while MLD_{TNGT} was a better predictor for RPT for the TNGT territory.

Key Words: Breast cancer, Radiotherapy, Pulmonary toxicity, Three-dimensional radiotherapy planning

Introduction

External beam radiotherapy (RT) is an important component of post-lumpectomy therapy in patients with breast cancer that wish to maintain breast conservation. It is also efficacious in the postmastectomy setting by increasing the rate of local-regional control and survival.[1~3] Both local and local-regional RT are generally well tolerated. Nevertheless, cardiopulmonary toxicity can arise from incidental irradiation

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of nontarget tissues in the vicinity of the breast/chest wall or of the regional lymph nodes.[4~6] Symptomatic radiation pneumonitis (SRP) has been a relatively rare complication in these patients, occurring 1~6 months after RT in approximately 0~29% of cases.[7~11] Limited data are available on the potential confounding effects of patient-specific and multimodality therapy factors such as age, smoking habits, sequential chemotherapy, and treatment with tamoxifen on the development of RT-induced lung damage.[12~15]

The ability to predict and quantify the risk of radiation pneumonitis has clear benefits both in reducing normal tissue complications, as well as in maximizing tumor control probability. It is challenging to relate quantitative dosimetric parameters to the subsequent development of pulmonary toxicity. In clinical studies, it has been common to report the incidence of lung toxicity in patient subgroups, defined by arbitrary cut points of the parameter. The total dose, the dose per fraction, and the incidentally irradiated lung volume primarily influence both the probability and severity of early and late RT-induced lung injuries. The exact tolerance dose of normal lung tissue is not fully known in humans, but previous reports suggest that it is in the order of 20~30 Gy.[16,17] It is unclear whether there is a linear/exponential correspondence between the irradiated lung volume and toxicity or whether a threshold value exists for the development of radiation pneumonitis.

In this study, we tried to evaluate the incidence and potential predictive factors for symptomatic radiation pneumonitis (SRP) and radiographic pulmonary toxicity (RPT) following adjuvant radiotherapy for patients with breast cancer. We particularly focused on the correlation of RPT with dose volume histogram (DVH) parameters obtained from the use of three-dimensional RT planning (3D-RTP).

Materials and Methods

1. Patient population

A review was performed of 184 patients irradiated to the breast/chest wall, with or without comprehensive nodal coverage between September 2003 and February 2006. Of the 171 patients initially included for evaluation in the study, 13 patients were excluded due to the following reasons: seven patients for follow-up loss, four patients with unavailable follow-up chest radiographs, one patient that received double primary lung cancer surgery immediately after RT, and one patient with the sternum included in the clinical target volume (CTV) due to a suspicious bone metastasis.

One hundred fifteen patients (67%) were treated with breast conserving surgery (BCS) and 56 patients (23%) underwent a modified radical mastectomy (MRM). The majority of patients (81%) received systemic chemotherapy before RT and 18% received neoadjuvant chemotherapy. A taxane-based chemotherapeutic regimen was used in 55% of the patients, with paclitaxel and docetaxel used in 38% and 17%, of the patients, respectively.

To improve the therapeutic ratio, three-dimensional RT planning (3D-RTP) (Pinnacle, Phlilips, Madison, WI, USA) was performed for all patients that received adjuvant RT since July 2004. Regional RT to the supraclavicular nodal area was indicated in 65 patients (38%). There was a large intrapatient variability in the height of the lung shadow in the superior

Table 1. Patients Characteristics

Characteristic (n)	n (%)
General (171)	
Age (years)	Range: 25~76 Median: 47
Smoking	5 (3)
Pre-existing lung disease	5 (3)
Surgery (171)	
BCS*	115 (67)
MRM†	56 (23)
Stage (171)	
0	23 (14)
I	48 (28)
II	44 (26)
III	56 (32)
Chemotherapy (112)	
Adjuvant	91 (81)
Neoadjuvant	21 (18)
Chemotherapeutic agent (112)	
Taxane based	61 (55)
Non-taxane based	51 (45)
Hormonal therapy (104)	
Tamoxifen	78 (75)
Aromatase inhibitor	26 (25)
RT technique (171)	
Conventional	34 (20)
3D-RTP‡	137 (80)
Regional RT (65)	
Conventional	6 (9)
3D-RTP	59 (91)

*breast conserving surgery, †modified radical mastectomy, ‡three-dimentional radiotherapy planning

and inferior aspect of the tangential fields. Furthermore, because of anatomic differences, there were marked inter-patient differences, as well. The incidence of SRP/RPT was reviewed. Others factors associated with RPT in previous studies were also reexamined. The patient characteristics are summarized in Table 1.

2. Treatment technique including RT planning

The postlumpectomy breast was typically treated with two opposing tangential 6 MV photon fields to a total does of 50 ~50.4 Gy (Clinac, Varian, Palo Alto, CA, USA). The tumor bed was generally treated with an additional 9~10 Gy by an en face electron field for patients with invasive carcinoma after BCS. The postmastectomy chest wall was treated in a similar fashion with tangential photon fields to a dose of 50.4 Gy. The supraclavicular fossa was treated with an anterior oblique photon field to a total dose of 50.4 Gy for N2 disease. The border between the tangential fields and the supraclavicular field was typically at the level of the inferior aspect of the clavicular head. Routine irradiation of the internal mammary lymph nodes was not applied because of concern about potential cardiopulmonary toxicity.

To evaluate the relationship with RPT, dose volume histogram (DVH) parameters including the overall percentage of ipsilateral lung volume that received ≥15 Gy (V_{15}), 20 Gy (V_{20}), and 30 Gy (V_{30}) and the mean lung dose (MLD) were calculated based on the cumulative DVH. Since irradiation for any one territory of either tangent portals (TNGT) or the supraclavicular portal (SCL) is unrelated with the development of RPT in another territory, we divided the ipsilateral lung into two territories. Separate dose volumetric parameters were defined, *i.e.*, $V_{15\ TNGT}$, $V_{20\ TNGT}$, $V_{30\ TNGT}$, MLD_{TNGT} versus $V_{15\ SCL}$, $V_{20\ SCL}$, $V_{30\ SCL}$, MLD_{SCL} to assess the possible association between these parameters and RPT.

3. Follow up evaluation of patients

All patients received follow-up by a radiation oncologist at one month after completion of RT, every three months for the first year, and 6 months thereafter. Serial follow-up chest radiographs were reviewed by a chest radiologist. RTOG toxicity criteria were used for grading SRP and a modified

Table 2. Modified WHO Grading System for Radiographic Pulmonary Toxicity

		Score
Area of ipsilateral lung involved (A)	None	0
	<1/3	1
	1/3~2/3	2
	>2/3	3
Degree of shadowing (S)	None	0
	Faint*	0.5
	Moderate†	1
	Dense†	1.5
Distortion of anatomy (D)	None	0
	Volume loss	2
Sum (A+S+D)		

*ground glass opacity only with well-visualization of normal anatomy, †degree of shadowing between faint and dense shadow, †patch or confluent opacity without visualization of normal anatomy

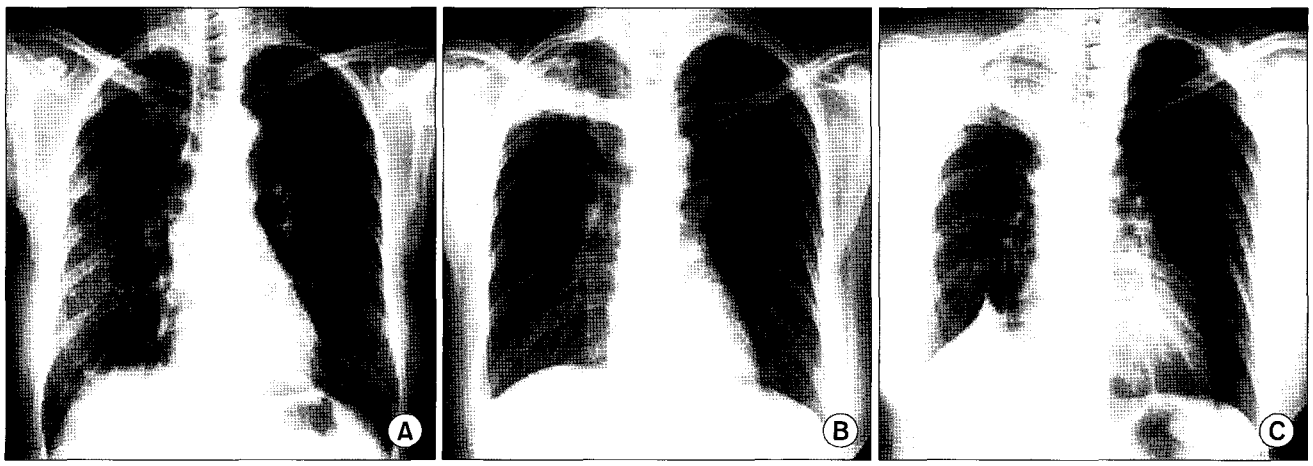

Fig. 1. Typical cases of radiographic pulmonary toxicity. (A) Area of ipsilateral lung involved >2/3 (score 3), (B) Dense shadowing (score 1.5), (C) Presence of volume loss (score 2).

WHO grading system was used to evaluate RPT. According to the RTOG toxicity criteria, patients with RTOG grade 2 or higher radiation pneumonitis were considered to have symptomatic radiation pneumonitis (SRP). A modified WHO grading system that was based on comprehensive scoring analysis of RPT area of ipsilateral lung, degree of shadowing, and distortion of anatomy was developed for evaluation of RPT (Table 2).[18~20] Fig. 1 shows typical cases of each grade of RPT.

4. Statistical methods

Statistical analysis was performed using SPSS software (release 12.0.1, SPSS Inc., Chicago, IL, USA). A Logistic regression analysis was used to identify potential risk factors for SRP or RPT. A simple linear regression analysis was applied to identify the correlation between the severity of RPT and SRP. Receiver operating characteristic (ROC) curves were generated to assess the predictive ability of individual DVH parameters for the development of RPT. The probability of chance occurrence of less than 0.05 was regarded as statistically significant.

Results

1. Symptomatic radiation pneumonitis

Of 171 patients included in this study, only four patients (2.3%) developed SRP: three were classified as having RTOG grade 3 and one was classified as having grade 2. SRP was developed one month (1 patient), two months (2 patients), and three months (1 patient) after completion of RT. All patients complained of dry cough and dyspnea and/or low-grade fever with associated radiographical evidence of pneumonitis. Three patients with SRP were resolved with supportive care with or without steroid therapy and one of the grade 3 SRP patients required hospitalization. Three of the patients received regional RT to the supraclavicular nodal area, and two of the patients received taxane-based chemotherapy. Two of the patients were treated with 3D-RTP. In this study, we could not identify any clinical variable that was associated with development of SRP (Table 3).

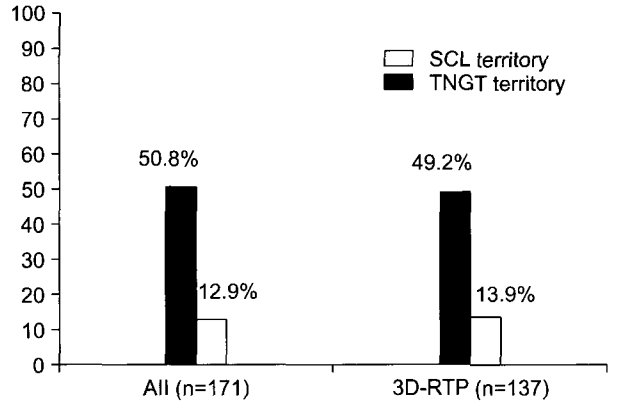

Fig. 2. Incidence and distribution of radiographic pulmonary toxicity (RPT).

2. Radiographic pulmonary toxicities

Four patients developed SRP that required steroid therapy. Forty-five patients showed RPT from the review of the serial

Table 3. The Relationship between Clinical Variables and Symptomatic Radiation Pneumonitis (SRP) or Radiographic Pulmonary Toxicity (RPT) (Forward Stepwise Logistic Regression Analysis)

Variable	SRP			RPT		
	OR*	95% CI†	p	OR	95% CI	p
Age			NS	1.046	1.002~1.092	0.039
Pre-existing lung disease			NS			
Smoking			NS			
Chemotherapy			NS			
Hormonal therapy			NS			
Regional RT			NS	10.323	4.534~23.501	<0.001
3D-RTP‡			NS			

*odds ratio, †confidence interval, ‡three dimentional radiotherapy planning

Table 4. Dose Volume Histogram (DVH) Parameters Based on 3 Dimensional Radiotherapy Treatment Planning

Territory	DVH parameter	95% CI (Gy)
Overall	V_{15}	21.4±1.7
	V_{20}	19.0±1.6
	V_{30}	15.5±1.4
	MLD	10.3±0.7
TNGT	$V_{15\ TNGT}$	14.0±0.7
	$V_{20\ TNGT}$	13.3±0.7
	$V_{30\ TNGT}$	10.6±0.7
	MLD_{TNGT}	7.5±0.3
SCL	$V_{15\ SCL}$	14.3±1.0
	$V_{20\ SCL}$	13.5±1.0
	$V_{30\ SCL}$	11.4±1.0
	MLD_{SCL}	6.7±0.4

*$V_{x\ TNGT}$: percentage of ipsilateral lung volume covered by TNGT >x Gy, $V_{x\ scl}$: percentage of ipsilateral lung volume covered by SCL >x Gy, †mean lung dose

chest radiographs. The incidence of RPT in TNGT were 12.9% of the initial 171 patients and 13.9% of the 137 patients that were subjected to 3D-RTP, respectively. The incidence of RPT was much higher in patients that received regional RT to the supraclavicular node area: 50.8% in all 65 patients and 49.2% in the 59 patients subjected to 3D-RTP, respectively (Fig. 2). Of all clinical variables, regional RT ($p < 0.001$) and age ($p=0.039$) were significantly associated with RPT by a forward stepwise regression analysis (Table 3). In a simple linear regression analysis, a statistically significant association was found between SRP and the summed RPT score ($r^2=1.249$, $p<0.001$)(data not shown). No further statistical analyses were applied to evaluate relationship between the DVH parameters and SRP as only two patients treated with 3D-RTP developed SRP.

DVH parameters of the individual lung territories in detail based on 3D RTP are summarized in Table 4. All listed DVH parameters of the individual lung territories except $V_{15\ TNGT}$ showed significant associations with RPT in a simple logistic regression analysis. We planned to select one representative DVH parameter of the individual lung territories, which had the closest area under curve (AUC) value to 1 from the ROC analysis. Therefore, MLD_{TNGT} and $V_{15\ SCL}$ were selected as the representative DVH parameter of T_{TNGT} and T_{SCL}, respectively, even though they showed modest predictive capacities (Fig. 3). Those representative DVH parameters together with clinical variables were included in a stepwise logistic regression analysis for RPT in the SCL or TNGT territories. With increasing the age of patents, the incidence of RPT in TNGT territory was increased in its tendency. MLD_{TNGT} were statistically significant for RPT in the TNGT territory, while $V_{15\ SCL}$ was the only significant variable for

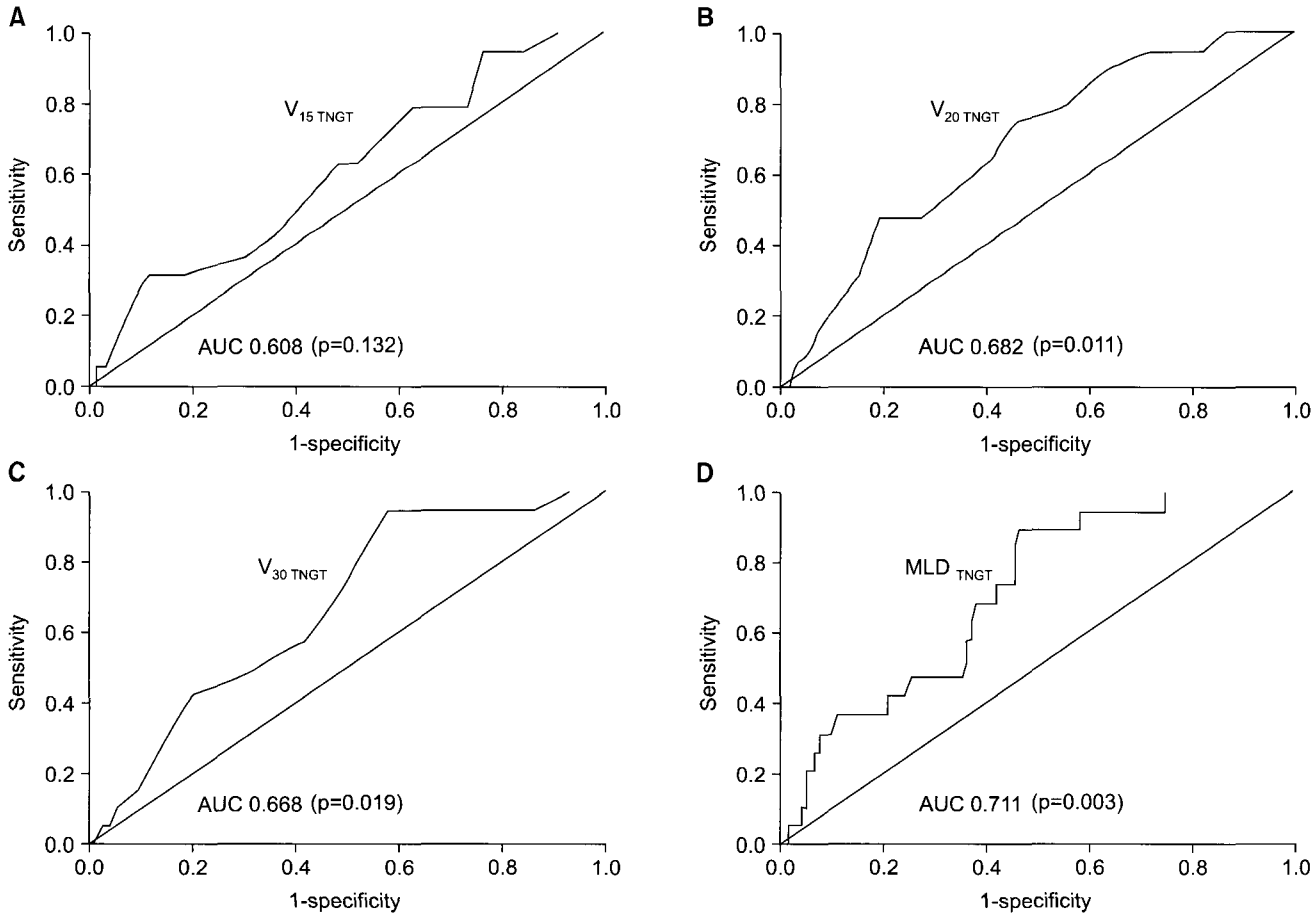

Fig. 3-I. Result of receiver operating characteristic (ROC) curve analysis for radiographic pulmonary toxicity (RPT) of tangent portals (TNGT)(I A-D) and supraclavicular portal (SCL)(II A-D) territories and corresponding DVH parameters. AUC: area under curve, $V_{x\ TNGT}$: percentage of ipsilateral lung volume covered by TNGT >x Gy, $V_{x\ scl}$: percentage of ipsilateral lung volume covered by SCL >x Gy, MLD_{y}: mean lung dose of TNGT or SCL territory.

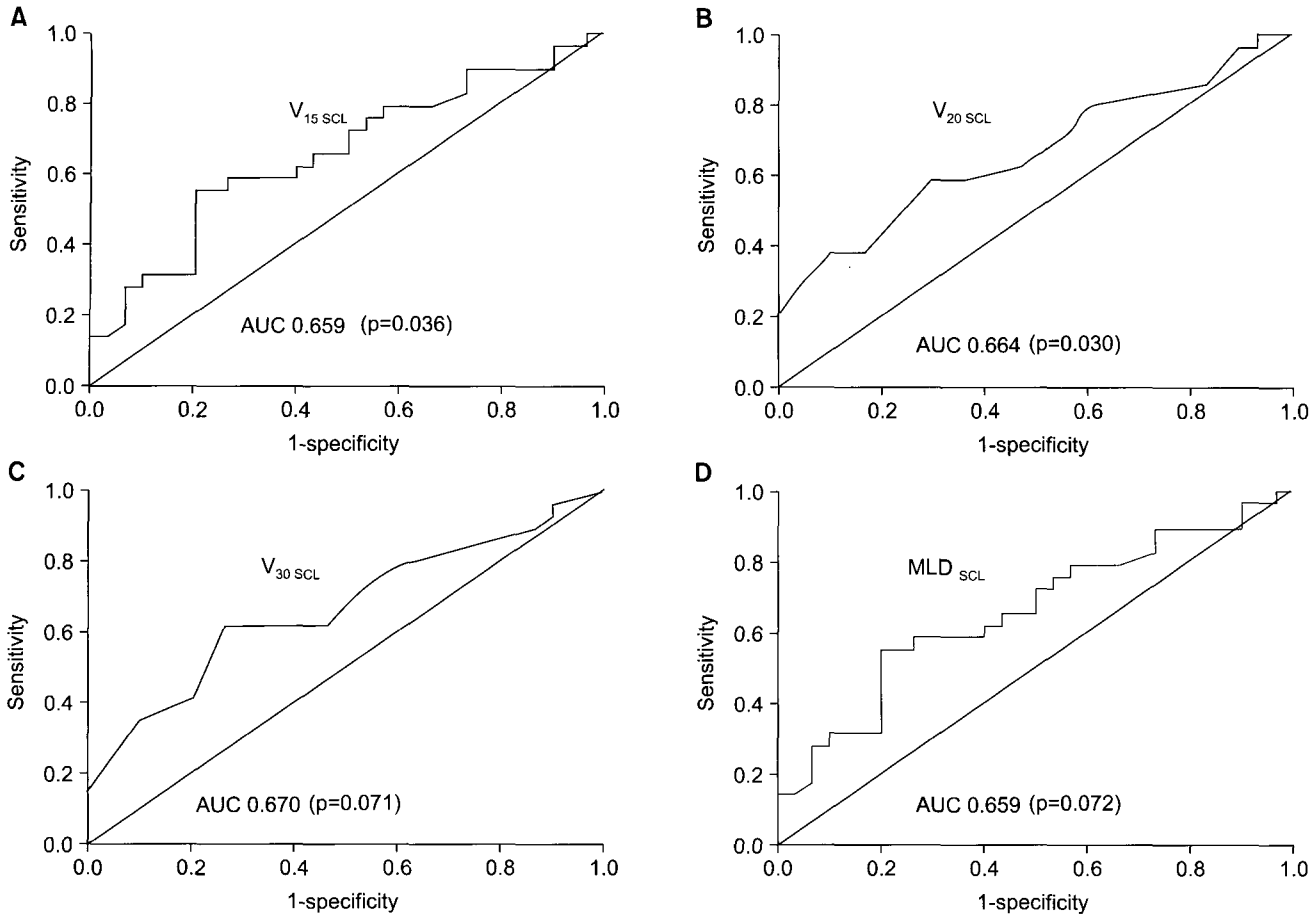

Fig. 3-II. Result of receiver operating characteristic (ROC) curve analysis for radiographic pulmonary toxicity (RPT) of tangent portals (TNGT)(I A-D) and supraclavicular portal (SCL)(II A-D) territories and corresponding DVH parameters. AUC: area under curve, $V_{x\ TNGT}$: percentage of ipsilateral lung volume covered by TNGT >x Gy, $V_{x\ scl}$: percentage of ipsilateral lung volume covered by SCL >x Gy, MLD_{y}: mean lung dose of TNGT or SCL territory.

Table 5. The Relationship between Clinical and DVH Parameters and Radiographic Pulmonary Toxicity (RPT) of Tangent Portals (TNGT) and Supraclavicular Portal (SCL) Territories (Forward Stepwise Logistic Regression Analysis)

Variable	TNGT territory			SCL territory		
	OR*	95% CI†	p	OR	95% CI	p
Age	1.062	1.008~1.118	0.024			
Pre-existing lung disease			NS			
Smoking			NS			
Chemotherapy			NS			
Hormonal therapy			NS			
MLD_{TNGT}§	1.441	1.103~1.882	0.007			
$V_{15\ SCL}$‖				1.201	1.037~1.391	0.014

*odds ratio, †confidence interval, ‡three dimentional radiotherapy planning, §mean lung dose of TNGT territory, ‖percentage of ipsilateral lung volume covered by SCL territory >15 Gy

RPT in the SCL territory (Table 5).

Discussion

Pulmonary toxicities following radiation therapy for thoracic malignancies are relatively common. Of the patients treated with radiotherapy for tumors close to the lungs, the patients with breast cancer consist of one of the largest groups and are also expected to be long-term survivors. Because of the adjuvant nature of postoperative radiotherapy in breast cancer, the extent and the severity of complications should be kept as low as possible. In this patients group, pulmonary complications can be divided into two major clinical syndromes: an early effect-radiation pneumonitis; and a later effect-

pulmonary fibrosis.[21~24]

Radiation pneumonitis after RT for breast cancer has been reported to be related to the following factors: the amount of the lung irradiated within the tangential fields,[11,25] the use of an additional supraclavicular field,[5] prior exposure to chemotherapy,[13,14] concurrent tamoxifen medication,[15] smoking habits,[26,27] and age.[14,27] In this study, regional RT and age were significantly correlated with RPT although we could not identify any clinical variable that was associated with the development of SRP probably due to the extremely small number of events.

In view of the therapeutic ratio, the optimal sequencing of radiation therapy and chemotherapy has been a long-term issue. Radiation therapy is usually administered after the completion of adjuvant chemotherapy, though in principle radiation therapy could be given before or concurrently with chemotherapy. Concurrent chemotherapy and radiation therapy remain an appealing clinical option for breast cancer and might improve local-regional treatment outcomes. A report from the M.D. Anderson Cancer Center suggests that sequential adjuvant taxane therapy followed by radiotherapy for breast cancer was associated with a 4~5% risk of clinically apparent pneumonitis.[28] Prior experience with cyclophosphamide, methotrexate, fluorouracil (CMF) therapy and concurrent chemotherapy was associated with only one case of radiation pneumonitis among 112 women receiving treatment.[29] However, these patients had Stage I or II breast cancer and received tangents only, without the addition of nodal radiation. There are several possible explanations for the apparent increase in pneumonitis; Because of clinical selection factors governing the use of taxane-based adjuvant chemotherapy, many women in this study were at a high risk for recurrence, with large tumors and/or multiple involved axillary lymph nodes. More than two-thirds of the patients had nodal irradiation, which by necessity increases lung exposure, and the pneumonitis tended to be more common in such patients, though the differences were not statistically significant, because of the small number of patients. It is not known whether limiting patient eligibility to low-risk patients receiving only tangential field radiotherapy might have led to different conclusions. A series from MGH have been reported that paclitaxel and concurrent radiation cannot be safely given after adjuvant cyclophosphamide, doxorubicin (AC) chemotherapy in terms of pulmonary toxicities.[13,30,31] Among women receiving standard dose taxane therapy as part of their adjuvant chemotherapy regimen, our practice remains sequential treatment with chemotherapy followed by radiation.

In the view of the evaluation of normal tissue complications following irradiation, the biophysical models describing dose-response relationships to include data from 3D-RTP represents an important tool in the calculation of normal tissue complication probabilities (NTCP), and consequently, in the evaluation and comparison of treatment plans. Despite the potential impact of NTCP modeling in radiotherapy, the data available for NTCP modeling is still scarce, and a consensus on the dose-response curves describing a specific endpoint for a specific organ has not yet been established.[32~34]

An alternative and efficient way to display and assess the predictive ability of a parameter/model throughout a range of cut points is the use of receiver operating characteristic (ROC) curves. ROC curves are regularly used in radiology studies but have not been applied frequently in the clinical field of radiation oncology.[35]

In this study, we evaluate the occurrence of RPT in relation to the dosimetric factors with the use of ROC curves. We first analyzed a patient dataset, consisting of the individual outcomes and the individual lung DVHs and tried to determine the optimum parameters. Second, the optimum parameter set was then used to evaluate a correlation with RPT. Age and MLD_{TNGT} were statistically significant for RPT in the TNGT territory, while $V_{15\ SCL}$ was the only significant variable for RPT in the SCL territory. All DVH parameters except $V_{15\ TNGT}$ showed a significant correlation with RPT ($p<0.05$); MLD_{TNGT} was a better predictor for RPT for the TNGT territory than $V_{15\ SCL}$ for the SCL territory.

In summary, the incidence of SRP was acceptable with the RT technique we used. Age and regional RT were significant factors to predict the development of RPT. The DVH parameter was a good predictor for RPT in the SCL territory while MLD_{TNGT} was a better predictor for RPT in the TNGT territory. Taken together, this study supports the predictive value of 3D RTP data for radiation induced pulmonary toxicities. Studies using conformal RT or intensity modulated RT for the whole breast or partial breast irradiation to minimize radiation induced cardiopulmonary toxicities are ongoing and reporting early promising results in terms of

pulmonary toxicities have been reported,[36] but these potential benefits still need to be defined.

References

1. **Overgaard M, Jensen MB, Overgaard J, et al.** Post-operative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen. Danish Breast Cancer Group DBCG 82c randomised trial. Lancet 1999;353: 1641-1648
2. **Overgaard M, Hansen PS, Overgaard J, et al.** Post-operative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997;337:949-955
3. **Ragaz J, Jackson SM, Le N, et al.** Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337:956-962
4. **Cuzick J, Stewart H, Rutqvist L, et al.** Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy [see comments]. J Clin Oncol 1994;12: 447-453
5. **Lingos TI, Recht A, Vicini F, et al.** Radiation pneumonitis in breast cancer treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys 1991;21: 355-360
6. **Lind PA, Wennberg B, Gagliardi G, et al.** Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. Breast Cancer Res Treat 2001; accepted pending revision.
7. **Gagliardi G, Bjohle J, Lax I, et al.** Radiation pneumonitis after breast cancer irradiation: analysis of the complication probability using the relative seriality model. Int J Radiat Oncol Biol Phys 2000;46:373-381
8. **Gaffney DK, Prows J, Leavitt DD, et al.** Electron arc irradiation of the postmastectomy chest wall: clinical results. Radiother Oncol 1997;42:17-24
9. **Price A, Jack WJ, Kerr GR, et al.** Acute radiation pneumonitis after postmastectomy irradiation: effect of fraction size. Clin Oncol (R Coll Radiol) 1990;2:224-229
10. **Rothwell RI, Kelly SA, Joslin CA.** Radiation pneumonitis in patients treated for breast cancer. Radiother Oncol 1985; 4:9-14
11. **Lind PA, Gagliardi G, Wennberg B, et al.** A descriptive study of pulmonary complications after postoperative radiation therapy in node-positive stage II breast cancer. Acta Oncol 1997;36:509-515
12. **Johansson S, Bjermer L, Franzen L, et al.** Effects of ongoing smoking on the development of radiation-induced pneumonitis in breast cancer and oesophagus cancer patients. Radiother Oncol 1998;49:41-47
13. **Taghian AG, Assaad SI, Niemierko A, et al.** Risk of pneumonitis in breast cancer patients treated with radiation therapy and combination chemotherapy with paclitaxel. J Natl Cancer Inst 2001;93:1806-1811
14. **Lind PA, Marks LB, Jamieson TA, et al.** Predictors for pneumonitis during locoregional radiotherapy in high-risk patients with breast carcinoma treated with high-dose chemotherapy and stem-cell rescue. Cancer 2002;94:2821-2829
15. **Bentzen SM, Skoczylas JZ, Overgaard M, et al.** Radiotherapy related lung fibrosis enhanced by tamoxifen. J Natl Cancer Inst 1996;88:918-922
16. **Hernando ML, Marks LB, Bentel GC, et al.** Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51:650-659
17. **Armstrong JG, Zelefsky MJ, Leibel SA, et al.** Strategy for dose escalation using 3-dimensional conformal radiation therapy for lung cancer. Ann Oncol 1995;6:693-697
18. **Lind PA, Svane G, Gagliardi G, et al.** Abnormalities by pulmonary regions studied with computer tomography following local or local-regional radiotherapy for breast cancer. Int J Radiat Oncol Biol Phys 1999;43:489-496
19. **Wennberg B, Gargliardi G, Sundbom L, et al.** Early response of lung in breast cancer irradiation: radiologic density changes measured by CT and symptomatic radiation pneumonitis. Int J Radiat Oncol Biol Phys 2002;52:1196-1206.
20. **Kim IA, Choi IB, Kang KM, et al.** Concurrent chemo-radiation therapy in stage III non-small cell lung cancer. J Korean Soc Ther Rad Oncol 1997;15:27-36
21. **McDonald S, Rubin P, Phillips TL, et al.** Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints and potential scoring systems. Int J Radiat Oncol Biol Phys 1995;31:1187-1203
22. **Movsas B, Raffin TA, Epstein AH, et al.** Pulmonary radiation injury. Chest 1997;111:1061-1076
23. **Freyer CJH, Fitzpatrick PJ, Rider WD, et al.** Radiation pneumonitis: experience following a large single dose of radiation. Int J Radiat Oncol Biol Phys 1978;4:931-936
24. **Mah K, Van Dyk J, Keane T, et al.** Acute radiation induced pulmonary damage: a clinical study on the response to fractionated radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:179-188
25. **Rothwell RI, Kelly SA, Joslin CA.** Radiation pneumonitis in patients treated for breast cancer. Radiother Oncol 1985; 4:9-14
26. **Bjermer L, Franze'n L, Littbrand B, et al.** Effects of smoking and irradiated volume of inflammatory response in the lung of irradiated breast cancer patients evaluated with bronchoalveolar lavage. Cancer Res 1990;50:2027-2030
27. **Theuws JC, Kwa SL, Wagenaar AC, et al.** Dose-effect relations for early local pulmonary injury after irradiation for malignant lymphoma and breast cancer. Radiother Oncol 1998;48:33-43
28. **Yu TK, Whitman GJ, Thames HD, et al.** Clinically relevant pneumonitis after sequential paclitaxel-based chemotherapy and radiation in breast cancer patients. J Natl Cancer Inst 2004;96:1676-1681
29. **Bucholz TA, Austin-Seymour MM, Moe RE, et al.** Effect

of delay in radiation in combined modality treatment of breast cancer. Int J Radiat Oncol Biol Phys 1993;26:23-35
30. **Taghian AG, Assaad SI, Niemierko A, et al.** Is a reduction in radiation lung volume and dose necessary with paclitaxel chemotherapy for node-positive breast cancer? Int J Radiat Oncol Biol Phys 2005;62:386-391
31. **Burstein HJ, Bellon JR, Galper S, et al.** Prospective evaluation of concurrent paclitaxel and radiation therapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for stage II or III breast cancer. Int J Radiat Oncol Biol Phys 2006;64:493-504
32. **Koh E, Sun A, Tran TH, et al.** Clinical dose-volume histogram analysis in predicting radiation pneumonitis in Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2006;66:223-228
33. **Lind PA, Marks LB, Hardenbergh PA, et al.** Techinical factors associated with radiation pneumonitis after local± regional radiation therapy for breast cancer. Int J Radiat Oncol Biol Phys 2002;52:137-143
34. **Gagliardi G, Bjohle J, Lax I, et al.** Radiation pneumonitis after breast cancer irradiation: analysis of the complication probability using the relative seriality model. Int J Radiat Oncol Biol Phys 2000;46:373-381
35. **Lind PA, Wennberg B, Gagliardi G, et al.** ROC curves and evaluation of radiation-induced pulmonary toxicity in breast cancer. Int J Radiat Oncol Biol Phys 2006;64:765-770
36. **Kahan Z, Csenki M, Varga Z, et al.** The risk of early and late lung sequele after conformal radiotherapy in breast cancer patients. Int J Radiat Oncol Biol Phys 2007 [In press]

국문초록

유방암 환자에서 보조적 방사선치료 후의 폐 손상

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목 적: 유방암 환자에서 보조적 방사선치료 후 호흡기 증상을 동반한 방사선 폐렴(SRP) 및 방사선학적 폐 독성(RPT)의 빈도 및 이에 영향을 미치는 예측인자를 알아보고자 하였다. 특히 3차원 방사선계획에서 얻은 선량체적히스토그람(DVH) 인자와 RTP의 상관관계를 중심으로 분석해보고자 하였다.

대상 및 방법: 2003년 9월부터 2006년 2월까지 171명의 환자가 유방암으로 수술 후 방사선치료를 받았다. 2개의 tangential photon 조사야가 통상적으로 사용되었고, 액와부 림프절 전이 정도에 따라 anterior oblique photon 조사야를 추가하였다. 유방 보존술 후 보조적 방사선치료를 받은 침윤성 유방암 환자에는 전자선을 이용한 boost가 적용되었다. 방사선 치료 후의 정기추적 흉부 단순촬영소견을 흉부방사선전문의와 함께 검토, 분석하였다. RTOG 특성기준 및 modified WHO grading system을 적용하였다. 조사받은 방사선량에 따라 V_{15}, V_{20}, V_{30} 및 mean lung dose (MLD)를 구하되, 동측 폐를 tangential 및 SCL 영역으로 구분하여, 각각의 DVH parameters 즉 $V_{15\ TNGT}$, $V_{20\ TNGT}$, $V30_{\ TNGT}$, $MLD_{\ TNGT}$ 및 $V_{15\ SCL}$, $V_{20\ SCL}$, $V_{30\ SCL}$, $MLD_{\ SCL}$을 구하여 RPT와의 상관관계를 분석하였다.

결 과: 호흡기 증상을 동반한 방사선 폐렴(SRP)이 4예(2.1%)에서 발생하였다(RTOG grade 3가 3예 grade 1이 1예). 나이 흡연여부, 기존폐질환유무, 항암요법, 호르몬치료, regional RT 여부 등은 SRP와 무관하였다. 3-RTP가 시행된 137예 중 13.9%에서 tangential 영역에 RPT가 발생하였다. Regional RT를 받은 59 중 49.2%에서 SCL 영역에 RPT가 발생하였다. Regional RT 유무($p<0.001$), 환자의 나이($p=0.039$), V15 TNGT를 제외한 모든 DVH parameter들이 RPT와 유의한 상관관계를 나타내었다. $MLD_{\ TNGT}$는 TNGT 영역의 RPT를, $V_{15\ SCL}$는 SCL 영역의 RPT를 예측하기에 적합한 것으로 분석되었다.

결 론: 본 연구에서 SRP의 빈도는 매우 낮았다. Regional RT 여부와 환자의 나이, DVH parameter들이 RPT와 유의한 상관관계를 나타내었으며, $MLD_{\ TNGT}$는 TNGT 영역에서, $V_{15\ SCL}$는 SCL 영역에서 RPT의 유의한 예측인자였다.

핵심용어: 유방암, 방사선치료, 폐손상, 3차원 치료계획