Mini Symposium - RT DOSIMETRY AND FRACTIONATION: Original Article

Abnormalities by pulmonary regions studied with computer tomography and clinical correlation following local-regional radiotherapy for breast cancer

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Abstract

Background: Adjuvant local-regional radiotherapy (RT) is commonly recommended for breast cancer patients. Postoperative adjuvant RT for breast cancer is associated with pulmonary side effects. This study was undertaken to measure the RT-induced pulmonary radiological changes with computer tomography (CT) scan using a CT-adapted modification of the Arriagada classification system, and to correlate these changes to RT techniques, pulmonary complications, and pulmonary function. The aim of the study is to study pulmonary radiological abnormalities with CT following different RT techniques for breast cancer, and their correlation to pulmonary complications and reduction in forced vital capacity (FVC). **Materials and Methods:** CT scans of the lungs were performed prior to and 4 months following RT in 53 breast cancer patients treated with local-regional RT. The radiological abnormalities were analyzed with a CT-adapted modification of a classification system originally proposed by Arriagada. The patients were monitored for RT-induced pulmonary complications. FVC was measured prior to and 6 months following RT. Statistical analysis used were that increasing CT scores were correlated with pulmonary complications ($P < 0.001$). The correlation between density grade (0-3, 4-9) and pulmonary complications (no complication vs slight/severe) was tested using Chi-square exact test for trend (2-sided). In addition, correlation between CT scores and FVC was done. **Results:** Increasing CT scores were correlated with pulmonary complications ($P < 0.001$). The mean reduction of FVC for patients scoring 4-9 (-220 ml) was larger than for patients scoring 0-3 (-15 ml) (Spearson correlation coefficient significant at 0.01 level 2 tailed). But the mean reduction of FVC with greater volume of lung irradiated was not statistically different than lesser volume of lung irradiated ($P > 0.05$). **Conclusions:** Radiological abnormalities detected on CT images and scored with a modification of Arriagada's classification system can be used as an objective endpoint for pulmonary side effects in postmastectomy RT.

Key words: Breast cancer, computerized tomography, pulmonary complication, pulmonary function, radiotherapy

Introduction

Postoperative radiotherapy (RT) for breast cancer plays an important role for reducing the rates of local recurrence and death. The treatment, however, delivers some unwanted irradiation to lung and heart. Side effects to the lungs are in the form of acute pneumonitis and sub acute/late lung fibrosis. The risk for acute and chronic RT-induced lung morbidity is influenced by total dose, dose per fraction and irradiated lung volume. When a 3 dimensional conformal radiotherapy (3D CRT) planning technique is used, it is possible to quantify and limit the amount of individually irradiated lung volume. Computerized tomography (CT) of the lung is a more sensitive technique than chest radiography for detecting RT-induced radiological abnormalities.[1] There is no

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accepted classification system for RT-induced radiological abnormalities. EORTC and RTOG have jointly proposed a system for the classification of radiological abnormalities in terms of lung density as one part of the late effects in normal tissues subjective, objective, management, and analytic *scales (LENT SOMA)* late effects in normal tissues subjective, objective, management, and analytic scale.[2] Both the definitions of target volumes and RT techniques differ among radiotherapy departments and it is, thus, important that data concerning side effects are presented together with at lung dose–volume histograms (DVH) for the used RT techniques. In 1989, Arriagada *et al.* presented a system for chest radiographs that also considers information about affected regions of the lung.[3] Little is known about the importance of the respective pulmonary regions in the development of pulmonary complications. It has, however, generally been believed that the apex of the lung is of limited importance due to the small relative lung volume and the low pulmonary blood flow in this region.[4-6] Little is known as to whether or not other factors than target volumes and RT techniques influence the development of RT-induced radiological abnormalities. Both sequential chemotherapy and concomitant tamoxifen treatment have been reported to enhance the development of RT-induced side effects.[7,8] This study was undertaken to measure the RT-induced pulmonary radiological changes with CT at 6 months following RT in 53 breast cancer

patients, using a CT-adapted modification of the Arriagada classification system, and to correlate these changes to RT techniques, pulmonary complications, and pulmonary function.

Materials and Methods

The study was a single institutional prospective study. This study was approved by the local ethics committee of our hospital. Participating women gave informed consent before study enrolment.

Study population

All women who were referred to the Radiotherapy Department at Medical College and Hospital during 2010 and 2011 for adjuvant loco-regional RT after surgery for early and late breast cancer were asked to participate in this trial. Fifty-five patients were included, but two patients did not consent to come for regular follow up and were not evaluable. Fifty-three patients were thus included and followed up for 6 months after RT for symptoms of acute/sub acute radiation-induced pulmonary complications. Mastectomy was done in all patients. Thirty-five patients were irradiated with locoregional radiation therapy (LRRT) to the chest wall, axilla, and supraclavicular region and in these patients the internal mammary lymph nodes (IMN) were included. A total of 18 patients received RT excluding the IMN.

The mean age of the patients was 56 years (range 32-81). The chemotherapy was concluded 3-4 weeks prior to RT. The typically regime consisted of doxorubicin, cyclophosphamide, and 5-fluorouracil, but in 14 patients the therapy included docetaxel. Intake of tamoxifen and anastrozole during RT was evenly split among the women.

RT treatment techniques

Dose planning was performed using the ASHA Teletherapy planning system (Release 3) and 16 Slice CT scan was performed with the CT simulator in our department.

Local-regional RT. The target volume was defined as the ipsilateral internal mammary, axillary, and supraclavicular lymph nodes and the chest wall. The prescribed dose to the chest wall and regional lymph nodes was 50 Gy (2.0 Gy/fraction, 5 fractions/week).

The chest wall clinical target volume (CTV) was outlined in each CT slice using the RTOG contouring guidelines. Nonpathological internal-mammary (IM) ± medial-supraclavicular (MS) lymph nodes can hardly be seen on CT data. With the aid of other visible structures, the IM ± MS CTV was defined. The CTV of the IM lymph nodes was assumed to be located around the internal mammary vessels. The IM ± MS planning target volume (PTV) was defined by expanding the CTV 5 mm in the anterior ± posterior direction and 10 mm in the medio-lateral direction.

Since, there is presently no provision of electron beam

therapy in our set-up, for treating internal mammary nodes, "deep tangent" technique, that is, tangent fields are brought across the midline of the patient to try to include the IMN inside the high-dose volume. The axillary and supraclavicular lymph nodes were treated with an anterior-posterior (AP) beam. All patients were planned in a supine position and treated by Cobalt[60] unit of Theratron 780C (Theratonics International, Kanata, Ontario, Canada).

Dose prescription

The treatment plans were normalized at the ICRU reference point. The International Commission on Radiation Units and Measurements (ICRU) reference dose was 2 Gy per fraction, with a total treatment dose of 50 Gy.

Data analysis

Dose volume histograms (DVHs) were computed for the chest wall and IM ± MS target volumes and for the lungs. For the chest wall PTV, the volume receiving at least 85% of the reference dose was calculated [Figure 1].

Evaluation of dose and lung volumes

In the present study all patients underwent 3-D dose treatment planning (ASHA Release 3) with avoidance of a dose exceeding 20 Gy to more than 30% of the ipsilateral lung volume at least in patients in which, IMN were exclude but with a good coverage of the CTV (PTV). Monitoring for symptomatic pneumonitis and evaluation of radiological pneumonitis on CT with the Arrigada's classification were done.

All patients were followed for respiratory symptoms, that is, cough, dyspnea with or without fever, 1, 4, and 6 months after the termination of RT.

All patients were, thus, classified into three groups as follows:

(1) No reaction: No registered respiratory symptoms (cough and/or dyspnea with or without fever) or respiratory symptoms judged by the clinician not to be caused by RT.

(2) Slight reaction: Respiratory symptoms judged by the

Figure 1: Computer tomography section showing dose distribution curves

clinician to be caused by RT but not treated with corticosteroids.

(3) Severe reaction: Same as (2), but treated with corticosteroids (prednisolone 60 mg/day po).

CT of the thorax was performed before and 6 months after RT and evaluated.

Evaluation of dose and lung volumes

Cumulative lung DVHs for two techniques used for local-regional RT are plotted. According to the lung DVH for following modified radical mastectomy excluding the IMN (*n = 18*) results in roughly 25% of the ipsilateral lung volume receiving a dose of 20 Gy or more [Figure 2]. Local-regional RT following modified radical mastectomy including the IMN (By deep tangent technique) (*n = 35*)) results in roughly 32% of the ipsilateral lung volume receiving a dose of 20 Gy. Furthermore, the central lung distance (CLD) was measured on the individual simulator films of the posterior tangential field for all the treatment techniques used. The CLD (i.e., the perpendicular distance from the posterior tangential field edge to the posterior part of the chest wall at the center of the field) provides an estimate of the percent of the ipsilateral lung treated by the tangential fields.[9] The mean CLD for cases, excluding the IMN, was 14 mm(range: 5–19 mm). while in patients, including the IMN, the mean CLD was 19mm (range: 15-21mm).

Evaluation with computer tomography and a modification of Arriagada's classification

CT was performed prior to RT and 6 months following cessation of treatment. On both occasions, slices on three levels of the lung were examined (i.e., the central CT slice, the slice just above the heart contour, and an apical slice at the level of the clavicle). The lung density on the treated side was examined using the standard lung window (mean 2600; width 1000 Hounsfield's Units). An increase in density was graded according to a C T-adapted modification of Arriagada's classification (i.e., 0 = no change; 1 = low opacity

in linear streaks; 2 = moderate opacity; 3 = complete opacity)[3] [Figure 3].

The lung was also divided into the three regions suggested by Arriagada (i.e., apical-lateral (A-L), central-parahilar C-P), and basal-lateral (B-L). The border between the A-L and B-L regions was set at the level of the pulmonary artery. The width of the C-P region was set to 5 cm. The highest density grade in each region was added together.

Total scores of 1-3 were considered to represent slight radiological reactions and scores ranging from 4 to 9 represented moderate to severe reactions.

Evaluation of pulmonary complications

The patients were regularly checked by a limited staff of experienced radiotherapists (four specialists) at 1, 4, and 6 months after the conclusion of treatment. Furthermore, trainees involved in the patients' care were instructed to consult a specialist in case of a suspected pulmonary complication.

At the 6-month check-up, a form was collected for each patient stating whether or not the patient during this follow-up period had been diagnosed with any RT-induced pulmonary side effects (i.e., cough and/ or dyspnea, with or without fever). According to the department routines, corticosteroids were recommended only to patients who were clearly impaired in their daily function.

Pulmonary function test

Pulmonary function tests were performed prior to and 6 months following the conclusion of RT in 81 patients. Forced vital capacity (FVC) was used for comparison.

Statistical methods

Chi-square exact test for trend (2-sided) was used to study the correlation between increasing CT scores and pulmonary complications.[10] The mean paired differences in FVC was compared for patients scoring 1-3 and 4-9 using Spearman's correlation coefficient test. Also the difference between FVC with two different volumes of lung (IMN included or excluded) were correlated by Fisher's exact test (2 sided).

Results

A total of 53 patients were evaluated by CT scores and pulmonary function test including FVC. Increasing
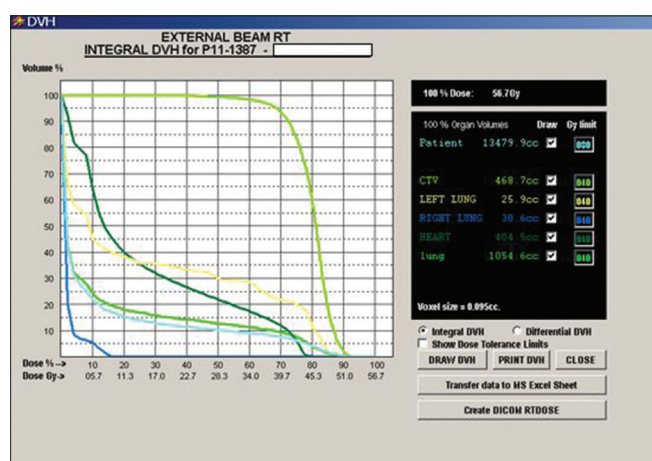

Figure 2: Dose volume histograms curve showing coverage of target and organ at risks
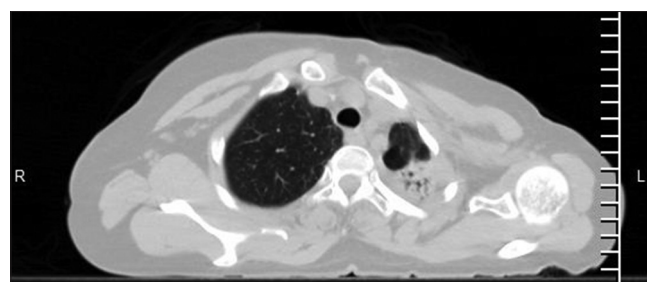

Figure 3: Severe radiation pneumonitis (score 3)

Table 1: Results of correlation tests between computerized tomography scores and pulmonary complications

CT scores	None	Pulmonary complications			
		Slight	Severe	Rate find (%)	
(0)	17	1	0	5.5	*P*<0.001*
(1-3)	14	6	0	30	
(4-9)	7	7	1	53.3	

*Chi-square exact test for trend

Table 2: Results of correlation tests between computerized tomography Scores and Forced vital capacity

Correlations			
Spearman's rho		**CT score**	**FVC reduction**
CT Score	Correlation coefficient	1.000	0.861**
	Sig. (2-tailed)	.	0.000
	N	34	34
FVC reduction	Correlation coefficient	0.861**	1.000
	Sig.(2-tailed)	0.000	.
	N	34	34

**Correlation is significant at the 0.01 level (2-tailed)

CT scores (0 and 1-3 and 4-9) were correlated with pulmonary complications (no vs slight and severe) [Table 1] ($P < 0.001$). The mean of the paired differences in FVC for patients scoring 4-9 (-220 ml) was larger than for patients scoring 0-3 (-15 ml) (*Spearman correlation coefficient significant at 0.01 level 2 tailed*) is shown in Table 2. The mean of paired difference in FVC for patients excluding IMN (97 ml) was not statistically different from that of patients including IMN (125 ml) ($P = 0.2176$).

Discussion

In this study, correlations between RT-induced radiological abnormalities and pulmonary complications/ loss of pulmonary function were found. We, therefore, conclude that radiological abnormalities detected on CT images and scored according to the CT adapted modification of Arriagada's classification system can be used as objective endpoints for RT-induced pulmonary complications in breast cancer. The described system should, however, be expanded and corroborated with information about the affected lung volume in each region before definite conclusions can be drawn concerning each region's relative importance for the development of pulmonary complications.

In 1991, Lingos *et al.* reported an increased incidence of radiation pneumonitis when a third field to treat the axillary/supraclavicular lymph nodes was added to the tangential fields treating the breast/chest wall.[11]

Recently, Overgaard *et al.* and Ragaz *et al.* reported an increased overall survival in high risk premenopausal breast cancer patients treated with a combination of chemotherapy and local-regional RT including the IMN, compared with chemotherapy alone.[12,13] The importance of the inclusion of the IMN in local-regional RT on overall survival is currently investigated in a randomized study performed by ESTRO. In conclusion, local-regional RT in breast cancer is still an optimization problem under investigation.

Still, in this study, other confounding factors like previous chemotherapy, smoking, etc., were not taken into account.

Whether or not sequentially administered chemotherapy can reduce the immune system's reactivity to irradiation need to be studied. In the article mentioned above, Lingos *et al.* also reported an increased incidence of radiation pneumonitis in patients treated with especially concurrent chemotherapy.[11]) Other investigators have claimed an increased incidence of radiation pneumonitis following sequential chemotherapy.[7]

In conclusion, we need to continue studying the effect of chemotherapy on RT-induced side effects in breast cancer patients.

In 1996, Bentzen *et al.* reported enhanced RT-induced pulmonary fibrosis on pulmonary radiographs in patients treated with concomitant tamoxifen.[8] This effect was not studied in our material and is yet to be studied.

Besides, there are other limitation of this study, the study being conducted in a single institution, the number of patients were less. Besides, we should compare the mean DVH, of a group of patients rather than computing the individual data of DVH. Further investigations for correlation with lobar volumes irradiated and complications thereof should be monitored. The long-term follow up of these pulmonary complications are also needed to be done.

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