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Cardiac and pulmonary side-effects of radiotherapy in early breast cancer

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av
Ulla Blom Goldman
Leg.läkare

Huvudhandledare:
Docent Pehr Lind
Karolinska Institutet
Institutionen för onkologi-patologi

Bihandledare:
Professor Per Hall
Karolinska Institutet
Institutionen för epidemiologi
och biostatistik

Bihandledare:
Docent Tommy Fornander
Karolinska Institutet
Institutionen för onkologi-patologi

Bihandledare:
Docent Gunilla Svane
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Fakultetsopponent:
Docent Johan Ahlgren
Uppsala Universitet
Centrum för klinisk forskning Gävleborg

Betygsnämnd:
Professor Crister Ceberg
Lunds Universitet
Medicinsk strålningsfysik

PhD Henrik Lindman
Uppsala Universitet
Institutionen för radiologi, onkologi
och strålvetenskaper

Professor Anders Sundin
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

From the DEPARTMENT OF ONCOLOGY-PATHOLOGY
Karolinska Institutet, Stockholm, Sweden

CARDIAC AND PULMONARY SIDE-EFFECTS OF RADIOTHERAPY IN EARLY BREAST CANCER

Ulla Blom Goldman

Karolinska Institutet

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“The minute you think of giving up, think of the reason why you held on so long”

ABSTRACT

The purpose of this thesis was to study early and late side-effects to lung and heart in adjuvant loco-regional radiation therapy (LRRT) of early breast cancer (BC). Papers I-III were intervention studies aiming to reduce symptomatic/ radiological pneumonitis and functional changes after LRRT by applying the ipsilateral lung dose volume constraint $V_{20} \leq 30$ %. The results were compared with a previous treatment series. Papers IV-V evaluated the long-term cardio-pulmonary effects of BC RT.

In paper I, 66 patients were followed for signs of post-RT pneumonitis and changes on chest computer tomography (CT) 4 months post-RT. Lung subvolumes with radiological changes were contoured and the mean doses were calculated. Few cases of symptomatic pneumonitis were diagnosed. The mean ipsilateral lung V_{20} was higher in symptomatic than in unaffected patients, 29 % vs 24 % ($p=0.04$). Mild/moderate radiological changes were detectable on chest CT in subvolumes with average doses > 30 Gy.

In paper II, patients were examined with chest X-ray and CT pre- and 4-5 months post-RT and compared to the outcome of our previous trial. The use of lung dose volume constraints significantly reduced moderate/severe radiological changes on chest X-ray compared with our earlier study ($p< 0.001$). Lung changes on CT were also limited in the present series and related to ipsilateral V_{13}.

In paper III, changes in pulmonary function tests (PFTs) were studied. The applied constraints appeared to lower short-term changes in PFTs. Pre-RT chemotherapy affected DLCO at baseline.

In paper IV, a long-term follow-up of irradiated women with BC, i.e. median 11 years, was undertaken. We assessed late changes in PFTs and radiological abnormalities with chest CT. The median matched VC, FEV1, and TLC were reduced 15, 9, and 7 %, respectively, compared to pre-RT values ($p<0.001$). DLCO, however, appeared to recover from baseline probably due to transient chemotherapy-induced lung toxicity. The median matched percentage of the predicted DLCO 11 years after RT was, however, only 86 %, indicating a chronic therapy-induced reduction also of this metric. The observed radiological and PFTs changes 4 months after RT were, thus, still detectable after a median follow-up of 11 years.

In paper V, the risk of developing ischaemic heart disease, through incidental heart irradiation, was examined in a population-based case-control study of 2,100 women, who underwent RT for BC during 1958-2001. Individual patient data were obtained and doses to the entire heart and left anterior descending coronary artery were estimated. Exposure of the heart to ionizing radiation during RT increased the subsequent rate of ischaemic heart disease. The increase was proportional to the mean dose to the heart, began within a few years after exposure, and continued for at least 20 years.

In conclusion, our aims to minimize incidental dose to lung in LRRT of BC lowered the short-term pulmonary side-effects and should therefore be utilized. The long-term studies showed that side-effects to lung and heart after adjuvant RT in BC with older techniques were of clinical relevance still after several years.

Key words: breast cancer, radiation therapy, pulmonary side-effects, ischaemic heart disease

LIST OF PUBLICATIONS

I. Blom Goldman U, Svane G, Wennberg B, Lideståhl A, Lind P. Quantitative assessment of lung density changes after 3-D radiotherapy for breast cancer. Acta Oncologica 2007;46:187-93

II. Blom Goldman U, Wennberg B, Bylund H, Lind P. Reduction of radiation pneumonitis by V20-constraints in breast cancer. Radiation Oncology 2010;5:99 http://www.ro-journal.com/content/5/1/99

III. Blom Goldman U, Anderson M, Wennberg B, Lind P. Radiation pneumonitis and pulmonary function with lung dose-volume constraints in breast cancer irradiation. Journal of Radiotherapy in Practice 2013; e-published

IV. Blom Goldman U, Svane G, Anderson M, Wennberg B, Lind P. Long-term functional and radiological pulmonary changes after radiation therapy for breast cancer. Acta Oncologica 2013; submitted

V. Darby S, Ewertz M, McGale P, Bennet A, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen M-B, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987-98

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Abbreviations

AI	Aromatase inhibitor
BC	Breast cancer
BED	Biologically effective dose
CI	Confidence interval
CT	Computer tomography
CTV	Clinical target volume
DVH	Dose volume histogram
EORTC	The European Organization for Research and Treatment of Cancer
FEV1	Forced expiratory volume in 1 second
Gy	Gray
IMN	Internal mammary lymph nodes
ICRU	International Commission on Radiation Units and Measurements
IHD	Ischaemic heart disease
LAD	Left anterior descending artery
LRRT	Loco-regional radiation therapy
MD	Mean dose
NCI-CTC	The National Cancer Institute Common Toxicity Criteria
NTCP	Normal tissue complication probability
OAR	Organ at risk
QoL	Quality of Life
RIHD	Radiation induced heart disease
RP	Radiation pneumonitis
RT	Radiation therapy
Tam	Tamoxifen

1. Aims of the studies

Study I. To study symptomatic and radiological pneumonitis in women with early breast cancer undergoing adjuvant loco-regional radiotherapy with lung dose-volume constraints.

Study II. To evaluate post-irradiatory radiological lung changes on chest X-ray and CT in relation to Quality of Life, common dosimetric factors, and co-variates in adjuvant loco-regional radiotherapy with lung dose volume constraints for early breast cancer.

Study III. To study changes in pulmonary function tests and symptomatic radiation pneumonitis after adjuvant loco-regional radiotherapy with lung dose volume constraints for early breast cancer.

Study IV. To evaluate long-term functional and radiological changes after adjuvant loco-regional radiotherapy without lung dose volume constraints for early breast cancer.

Study V. To estimate the risk of developing ischaemic heart disease after adjuvant radiotherapy in women with early breast cancer.

2. Introduction

2:1 Adjuvant radiotherapy in breast cancer

Breast cancer (BC) is a major global health problem among women with about 1.6 million new cases annually (1). The incidence is also increasing. In Sweden, more than 8,000 new cases were diagnosed during 2011 and 25 % of these were detected before 50 years of age. The median age at diagnosis was 64 years. The prognosis has, however, improved during the last decade and the survival rate is now greater than 80 %. Currently in Sweden, nearly 85,000 women are living as breast cancer survivors (2).

The treatment of primary breast cancer consists of surgery, adjuvant radiotherapy (RT), and systemic medical therapy, e.g. chemotherapy and endocrine treatment. Furthermore, new effective targeted treatments have been introduced during the last decade, e.g. trastuzumab. However, post-operative, adjuvant RT still remains one of the cornerstones to reduce the risk for local recurrence. It has been utilized since the 1930's and at the end of 1940's the first randomised, controlled trials of adjuvant RT were reported (3). With longer follow-up of these studies there was no survival benefit for the group receiving RT, instead a significant excess of non-breast cancer deaths was observed among these patients (4,5). Since then, several randomised trials and meta-analyses have shown a clinically significant reduction of local recurrences but no effect on overall survival. The beneficial effect of RT on survival was hampered by an increased risk of non-breast cancer deaths and analyses revealed that the largest cause was heart disease (6). Radiotherapy techniques and regimes have improved since these reports were published. Today, radiation exposure to the heart and lung is lower than they were in the earlier reports of the past. Thus, the latest meta-analysis and overview from EBCTCG in 2011 show a survival advantage for women receiving adjuvant radiotherapy compared to the unirradiated control group, i.e. the 15 year BC mortality decreased from 25.2 % to 21.4 % (absolute reduction 3.8 %). About one BC death was avoided by year 15 for every four recurrences avoided by year 10 (7).

2:2 Clinical target volume definition in breast cancer

The introduction of external megavoltage RT in the 1950's led to improvements in target delineation and dose homogeneity, but also led to the incidental irradiation of deeper-seated tissues. Tolerance doses for normal tissue to therapeutic irradiation were defined by Emami *et al* in the 1990's (8). In QUANTEC, Quantitative Analysis of

Normal Tissue Effects in the Clinic, we find the latest, updated overview and recommended dose/volume constraints (9). Computer tomography (CT) based RT planning in the 1980-90's has improved target volume visualization and multi-field and 3-dimensional (3-D) conformal RT are now regularly used. By using 3-D RT planning and multi-field treatment, irradiation to normal tissue and organ at risk (OAR) can to some extent be avoided. Dose distribution, volumetric data, and dose volume histogram (DVH) are calculated. Presently, guidelines for RT are provided by The International Commission on Radiation Units and Measurements (ICRU). The volumes that must be identified prior to RT are defined in the ICRU report 29 and updated in report 50 (10,11). In breast cancer treatment, the clinical target volume (CTV), or planning target volume (PTV), is usually defined by the oncologist. The PTV takes into account patient movements, breathing motion, and inaccuracies related to therapy equipment and positioning. The definition of the CTV has, however, changed during the last decade after the introduction of 3-D dose planning. Previously, the definition was mainly made with respect to the bony anatomy. The CTV after breast conserving surgery is now defined as the remaining breast parenchyma with or without the loco-regional lymph nodes. The target volume after mastectomy is defined as the chest wall corresponding to the previous extension of the breast. The regional lymph nodes are defined as the ipsilateral axillary and supraclavicular nodes. Previously, the internal mammary lymph nodes (IMN) have in most of the Nordic Centres been included in the target volume. Currently, many centres have excluded RT to the lower IMN to avoid lung and cardiac toxicity. A recent meta-analysis in Lancet 2005, however, demonstrated a benefit for RT after mastectomy in women with BC and positive lymph nodes and the majority of these women received RT to the lower IMN, i.e. in 21 of 23 trials (6). The randomised EORTC 22922/10925 trial, which tests the need for lower IMN irradiation, reports after three years of follow-up that RT to the IMN and medial supraclavicular nodes is well tolerated and does not impair the WHO performance status (12). Longer follow-up is, however, needed to determine excess cardiac toxicity and effect on overall survival. At ASCO 2011, Whelan *et al* reported a benefit for RT to the IMN in terms of reduction in distant recurrences, but also a small increase in rates of symptomatic pneumonitis (13).

2:3 Radiotherapy-related heart and lung side-effects

The aim of adjuvant RT is to eradicate left behind tumour cells without causing damage to the normal tissue, which can be described with models on Tumour Control Probability (TCP). Radiation therapy is also associated with side-effects in the treated

volume. By increasing the radiation dose to the target we will also increase the probability of damage to the surrounding normal tissue, which can be described with models on Normal Tissue Complication Probability (NTCP). Small difference in dose can have major biological effect (14).The therapeutic ratio is the ratio between the TCP and the NTCP (15,16). The radiotherapy schedules have been developed to maximize cure and to minimize the toxicity to normal tissue.

Side-effects of RT develop mainly locally in the irradiated volume. The side-effects are classified as acute/early or late effects. Early effects may occur during or immediately after treatment in hours-days-weeks in rapidly proliferating tissue, e.g. the hematopoietic system as effects on blood cell counts, skin as erythema, and lung as acute pneumonitis. Late reactions may appear months or years after treatment, e.g. subcutaneous fibrosis, lung fibrosis (17), teleangiectasia, rib fractures (18), and brachial plexus neuropathia (19,20).The development of arteriosclerosis may be triggered by radiation exposure (21). Radiation-induced late cardiac effects, e.g. ischaemic heart disease, have been known for some decades, and have been studied in earlier projects. Women irradiated to the left breast during 1970-85 in the Stockholm Trial developed an increased risk of myocardial infarction (MI) compared to women treated for right-sided BC (22). Paszat and colleagues found similar results with higher risk for fatal MI among patients treated for left-sided BC during 1982-7 (23). Furthermore, Hooning found an increased risk in smokers and RT to tumours on the left side (24).

2:4 Rationales of the studies

Many women with BC have a long expected survival. Radiotherapy is often used in the adjuvant setting. The vast majority will live many years after RT as BC survivors. It is therefore of great importance to minimize the side-effects of RT, and to investigate the long-term effects in lung and heart.

Papers I-III were intervention studies, in which an ipsilateral lung dose-volume constraint of $V_{20} \leq 30$ % was applied. We aimed to reduce early symptomatic/ radiological pneumonitis and loss of pulmonary function compared with our previous work in this field Lind, (25-29). The chosen cut-off level was based on our previous finding that no case of moderate symptomatic pneumonitis (CTC grade 2; (30) was detected below this threshold (26).

With respect to Paper IV: There are few data on the long-term effect of early radiation-induced radiological lung abnormalities and functional changes. There are some indications that fibrosis is a continuous process (31) and that symptoms can be

develop/worsen late (32). Due to the scanty data, we therefore wanted to re-examine the women from our earlier cohort of 1994-8 to see if the earlier detected changes diminished or worsened.

The term Radiation Induced Heart Disease (RIHD) was introduced in the 1960's. Long-term follow-up in some trials had shown that RT could increase the risk of ischaemic heart disease (5). Due to changes in RT-techniques and planning, the doses to the heart are now generally lower than the doses in the earliest meta-analyses and trials on BC-irradiation. The relation between low dose radiation exposure and the development of radiation-related heart diseases is, however, still not fully known. A population-based case-control study with collaboration between Denmark, Sweden, and Oxford was therefore conducted and reported in Paper V.

2:5 Definitions of the study populations

Study I-III consisted of 88 patients referred to the Radiotherapy Department during 2003-5 for adjuvant LRRT. In Study I, we report on RT-related radiological lung density changes and rates of clinical radiation pneumonitis in 66 of these patients. In Study II all 88 patients underwent chest X-ray and CT. Patients with radiological changes were compared with non-responders. Study III reported on pulmonary function tests (PFTs) in 64 of these patients.

Study IV consist of seventy women from our previous cohort who received RT for BC between 1994-8 and were included in our earlier reports (26,28). These women were now re-examined with chest CT and PFTs after a median period of 11 years. Fifty-six women performed repeated PFTs. Eleven women abstained from participating.

Study V was a population-based case-control study of major coronary events in 2,168 women who received RT for BC between 1958-2001 in Sweden and Denmark. The study included 963 women with major coronary events and 1,205 controls. Patient data were obtained from hospital records and RT-charts and the different RT-techniques were reconstructed.

3. Radiobiology and fractionated radiotherapy

Deposition of energy results in molecular damages in cells. The most important damages are double-stranded breaks in genomic DNA which cause cell death. Damage can also be inflicted indirectly in the cell by the ionization of water to hydroxyl radicals that cause single-stranded breaks. These result in sterilization, and loss of proliferative cells to sustain cell division. Proliferative sterilization is often referred to as cell kill. Cells that retain long-term proliferative ability are described as the survival fraction (33).

The Strandquist plot:

Magnus Strandquist was one of the first to describe the relation between the radiation dose necessary to achieve a certain biological effect and time during which the fractional treatment was in progress (Acta Radiol 1944). He introduced the log dose vs log time curves, viz. the Strandquist curves. Both the biological effect on the tumour as well as on the surrounding tissues were studied (34).

The linear quadratic (LQ)-model:

The Linear-Quadratic model was proposed by Douglas and Fowler in 1976 and it is based on a linear quadratic cell survival curve as a function of dose. It aimed to indicate quantitatively the biological effect of any RT-treatment, taking into account changes in dose-per-fraction or dose rate, total dose, and overall time (35).

$$S = e^{-(\alpha d + \beta d2)}$$

The Biological effective dose:

The biological effective dose (BED) is useful to compare the effect of different fractionation schedules. The possibility of complete repair of sublethal damage between fractions is assumed. The term was introduced in 1989.

$$BED = nd\,[1 + d/(\alpha/\beta)]$$

Number of fractions (n)

Dose per fraction (d)

α/ß defines the shape of the cell survival curve

Early and late responding tissues:

Radiobiological principles have gradually emerged over many years, and the

differences between late-responding normal tissues and early-responding normal and tumour tissues were clarified in the mid 1980's. The tissue-specific α/β-ratio is reflected by the shape of the dose-response curve. Stem cells of late responding tissues have low α/β-ratios.

Normal tissues are considered to have α/β-ratios around 3. Acute responding tissues have higher α/β-ratios and tumours are considered to have values around 10 Gy. Lung and heart have α /ß-ratios of 3 Gy and 2 Gy, respectively.

4. Pathogenesis and histopathology of radiation-induced injury to lung and heart

Alveoli are the terminal portions of the bronchial tree and are responsible for the spongy structure of the lung. The wall of the alveoli is composed of a single layer of type I and type II pneumocytes, and endothelial cells. Type I cells cover 90 % of the alveolar surface and type II pneumocytes are the replicator precursors of type I cells. Type II pneumocytes produce surfactant, and a decrease of this production results in transudation of serum proteins into the alveoli. Between the alveoli there are thin layers of connective tissue and numerous capillaries (36,37). The primary function of the lung is to provide oxygen to and extract CO_2 from the circulation. Radiation-induced lung injury comprises two syndromes:

Early phase, days/weeks, radiation pneumonitis:

Radiation injury to epithelial and endothelial cells in the lung causes a cascade of events and involves the expression of inflammatory cytokines. The result is alveolar collapse and interstitial inflammation. This may happen days or weeks after irradiation. The cells show cytoplasmic swelling and degenerative changes and this causes increased capillary permeability and occlusion of the microvasculature by platelets, fibrin, collagen, and debris from dead cells. A series of open-lung biopsies from the field of irradiation in patients with clinical pneumonitis suggested lymphocytic infiltration as the dominant finding in the acute phase (38).The lymphocytic alveolitis is confined to the irradiated volume but there are suggestions of widespread inflammation also in the surrounding, un-irradiated lung tissue. In the last years, broncho-alveolar lavage (BAL) has been used in the diagnosis of RP (39). Rarely observations are made of bronchiolitis obliterans with organizing pneumonia (BOOP) (40). The latter entity could arise months after RT and can be localised outside the RT-field. Mild RT-induced pneumonitis may be subclinical and reversible.

Late phase, months/years, radiation fibrosis:

Later, an organizing stage occurs, which includes the development of interstitial fibrosis. This phase has been widely documented in animal models. Pulmonary radiation reduces micro vessel density and lung perfusion, and promotes hypoxia. These effects may contribute to long-term damage, chronic inflammation, and late lung injury. This Radiation-Induced Lung Injury (RILI) may be regarded as a continuous progression of events. According to Graves, a hypothesis is that RILI is a result of an abnormal healing response in three phases: injury, inflammation, and repair (31). Pre-

clinical studies suggest a role for transforming growth factor beta (TGF-ß), interleukin-6 (IL-6), and other cytokines in the development of RILI (41). TGF-ß1 is the pro-fibrotic cytokine that causes fibroblast differentiation, senescence, and collagen production. Patients with lung cancer and persistent high serum levels of TGF-ß before and during RT for lung cancer had higher risk of developing pneumonitis than those with lower levels (42).

The main syndromes of RT Induced Heart Disease (RIHD) include inflammation and fibrosis. All structures can be affected. The most common manifestations are pericarditis, myocardial fibrosis, and coronary artery disease. Multiple studies in humans and laboratory animals have shown that irradiation can cause arteriosclerosis. Radiotherapy causes both acute and chronic changes in the heart tissues. The acute phase is characterized by a neutrophilic infiltrate in all layers of the heart within days after irradiation. Damage to the endothelial cells in arteries and capillaries can lead to luminal narrowing, perfusion defects, and ischemia (43,44). The adventitia is thickened and fibrotic in radiation-induced Coronary Artery Disease (CAD) compared with ordinary CAD (45).

5. Treatment of radiation-related injury to lung and heart

Lung:

Symptoms of RP are non-specific and include cough, i.e. non-productive or clear sputum, low grade of fever, dyspnoea, fatigue, and pleural chest pain. Lung auscultation may reveal crackles or a pleural rub. Chest X-ray changes are non-specific but typically confined to the irradiated volume. Airspace opacities are the most common finding. Pleural effusions or atelectasis are sometimes seen. Treatment with high-dose corticosteroids and antibiotics, e.g. tetracyclines, should start as soon as the diagnosis of RP is established. Steroids should be gradually reduced over weeks. If steroids are tapered too soon or too quickly, exacerbation of symptoms has been reported (46,47). Prophylactic administration of corticosteroids has been shown to decrease the physiological effect of radiation in mice. However, in humans this approach has failed to prevent the development of RP (48). No clinical benefit has been observed for treatment with steroids during the late stage of fibrosis (48,49). Pre-clinical studies have assessed the effect of captopril, an angiotensin-converting enzyme inhibitor, and this drug appears to reduce RT-induced lung fibrosis in rats (50). The combination of pentoxyfylline, a methylxantine derivate, and vitamin E, reduces RT-induced superficial and deep cervico-thoracal fibrosis, which earlier was considered irreversible in patients irradiated for breast or head and neck cancer (51,52). Amifostine, a sulfhydryl compound, believed to scavenge harmful free radicals that cause lung injury, has demonstrated inconsistent effects in clinical studies, and must be administrated concurrently with RT to be effective (53,54). Berberine, an alkaloid that exhibits anti-inflammatory activity and reduces the level of TGF-ß, has in clinical studies decreased RILI and improved pulmonary function in patients with NSCLC undergoing RT (55).

Heart:

There are no specific therapies or guidelines for treating RT-induced heart injury. Acute and chronic pericarditis is relatively uncommon but may sometimes occur. The patient may present with fever, pericarditis pain, dyspnoea, and tachycardia. Treatment includes the use of non-steroidal anti-inflammatory agents. A pacemaker can be indicated if the conduction system is affected. There are no specific therapies for radiation induced heart failure. The therapy should follow the College of Cardio / American Heart Associations Guide Lines according to Jaworski (56). The pro-

phylactic treatment of risk factors has been discussed, e.g. hyperlipidaemia with statins. In case of flow limiting coronary artery disease, medical therapy or re-vascularization can be indicated. The treatment of manifest radiation-induced coronary artery disease is not different to that of atherosclerotic origin (57). Screening for risk factors, especially in young patients, and treatment of diabetes, hypertension, hyperlipidaemia, and cessation of smoking should be recommended.

6. Factors influencing lung and heart tissue reaction to radiotherapy

6:1 Radiotherapy-associated factors

Variations in normal tissue reaction have been observed since the earliest day of RT. Factors related to the probability and severity of toxicity are type of radiation, total dose, dose per fraction, irradiated volume, irradiated site, and dose inhomogeneity. Toxicity from RT is in BC RT generally limited to the treated volume. The prescribed radiation dose to the breast or chest wall in BC RT is higher than the tolerance dose of lung.

Dose-effect relations in single fraction total thoracic irradiation:

The single fraction threshold dose for radiation pneumonitis starts at 7.5 Gy in total thoracic irradiation according to Dyk *et al.* They observed a steep dose-response relation that rose from 5 % to 50 % complication probability with an elevation of the single dose from 8.2 to 9.3 Gy (58).

Dose-effect relations in fractionated total thoracic irradiation:

Emami *et al* have compiled tolerance data for organs at risk and proposed that a total dose to the thorax of 24.5 Gy would lead to a 50 % probability of pulmonary complications in 5 years (tolerance dose TD 50/5) with conventional fractionation of daily 1.8-2.0 Gy 5 days a week. QUANTEC recommends that the volume fraction of the lungs that exceeds 20 Gy should be restricted to 30 %. This will give a probability of symptomatic pneumonitis of less than 20 % in standard clinical fractionation (9).

Effects according to fraction dose for irradiation to partial lung volumes:

Overgaard and co-workers reduced the fractions and increased the dose from 2 to 3 Gy in post-mastectomy RT between 1978 - 81. The incidence of both RP and lung fibrosis increased among women treated with this higher fraction dose compared with a conventional fraction schedules (59). There are also data from randomised studies comparing hypofractionated RT with doses > 2 Gy to conventional RT. Whelan *et al* presented 10 year results of comparing 2.66 Gy to 42.4 Gy with conventional fractionation of 2 Gy to 50 Gy. There was no difference in normal tissue complication or increase in toxic effects in the group receiving hypofractionated RT. Other studies, START-A and START-B (Standardisation of breast radiotherapy), compared conventional doses with 3.2 Gy to a total dose of 41.6 Gy, 3 Gy to 39 Gy, and 2.66 Gy to 40 Gy. No difference in cosmetic outcome compared to conventional fractionation was detected (60).

Dose-effect relations in fractionated cardiac irradiation:

Pericarditis was the chosen heart toxicity end-point in the Emami paper (8). Information from whole heart irradiation comes mostly from patients treated for Hodgkin's disease, whilst partial volume irradiated data come from post-operatively treated BC patients. A total dose of 40 Gy to the entire heart leads to a 5 % probability of heart complications in 5 years (TD 5/5). QUANTEC recommends that the volume fraction of the heart that receives ≥ 10 Gy should be restricted to 25 % for whole heart irradiation. The latter constraint will lead to a risk for long-term cardiac mortality of < 1 % (16).

6:2 Intrinsic factors

Individual differences in radiosensivity:

There is a significant individual variation in radiosensivity among patients. This is likely due to genetic differences (14,61). Patients with ataxia telangiectasia, a rare hereditary disease, have a high incidence of malignancies and both the tumour and normal tissue are exquisitely sensitive to ionizing radiation in these individuals (62). Results from studies identifying genetic factors associated with radiosensivity would help to predict which patients have increased risk for complications (63,64). RAPPER, Radiogenomics: Assessment of Polymorphisms for Predicting the Effect of Radiotherapy, is a large multicenter study addressing this issue (65).

Age:

Various results have been published concerning the influence of age on RT-induced toxicity. There are data from a Danish study with 8 years of follow-up after treatment for Hodgkin's disease. Patients with low age (< 30 year) at therapy had more restrictive lung disease in the follow-up (66). Other previous studies have, however, reported an increased risk of pneumonitis in breast cancer patients of advanced age (27,28). Gagliardi *et al* (67), Kahan *et al* (68) also found a higher risk of lung complications with increased age in BC patients. The functional reserve of the lung is age dependent and decreases in the elderly as the elasticity in the lung decreases, which reduces the ability to compensate for RT-induced injury. In contrast, Hardman *et al* found no association between age and pulmonary injury in BC patients (69). In a literature-based meta-analysis in 2012, 4/31 studies including BC patients, Vogelius and Bentzen found a significant risk for pneumonitis in older patients, i.e. 57 to 70 years of age (70).

6:3 Extrinsic factors

Pre-existing lung and heart disease:

Patients with pre-existing lung disease and poor pulmonary function have a low capability to compensate for radiation injury (71). It is not known whether the lung tissue is more sensitive to RT in this group. Poor performance status was another potential risk factor for RP in the above mentioned meta-analysis by Vogelius and Bentzen (70).

Pre-existing ischaemic heart disease is a risk factor for RT-induced IHD (72,76).

Other co-morbidities:

Vascular and connective tissue diseases are a heterogeneous group of diseases which have been considered a relative contraindication for RT due to sporadic reports of increased treatment toxicity (73,74). Li *et al* reported results on seventy-three patients with different connective tissue diagnoses. They found no difference in acute side-effects compared to a normal population but more late complications (75).

A history of ischaemic heart disease, hypertension, or diabetes and high BMI increase the risk for major coronary events after RT according to King *et al* (76).

Atherosclerosis:

The development of atherosclerosis can be triggered by radiotherapy and it is a risk factor for RT-induced IHD (77) .

Smoking:

Smoking and poor pulmonary capacity at baseline may predict for an increased risk of pneumonitis.

Smoking decreases the diffusions capacity of lung due to pulmonary vasoconstriction (78,79). Smoking may, however, protect both tumour and normal tissue from acute radiation effects (80,81,82). The suggested mechanism is that smoking suppresses the local inflammatory reaction in the lung (83). However, in a Danish study in patients with Hodgkin's disease smokers had reduced lung function compared to non-smokers 8 years after thoracic irradiation (66).

Radiotherapy and smoking had an additive effect on the risk of myocardial infarction in BC patients (84).

Concurrent chemotherapy:

It is known that certain chemotherapeutic agents have synergistic interaction when given concurrently with RT. A number of cytotoxic drugs have been investigated, on this matter, both in vivo and in vitro, e.g. methotrexate, bleomycin, doxorubicin, cyclophosphamide, docetaxel, and gemcitabine. They are all known to cause

pulmonary toxicity by local inflammation. Taghian *et al* have reported an increased incidence of RP in women treated for BC with chemotherapy combinations including paclitaxel, concurrently or sequentially, with RT (85, 86). Anthracyclines significantly added to the elevated risks of congestive heart failure and valvular disorder from mediastinal RT in Hodgkin's disease (87). However, most data on this topic are based on experience from other diagnoses than breast cancer (48, 88-90).

Concurrent tamoxifen, aromatase inhibitors:

Tamoxifen has been reported to influence the risk of post-RT fibrosis. Some studies suggest that tamoxifen induces secretion of TGF-ß that effects the development of fibrosis (91).

Aromatase inhibitors, viz. letrozole, and RT have been evaluated in a randomized trial in BC and the combination has been considered to be safe with respect to short-term toxicity. There are, however, no long-term data and a subtile radiosensitizing effect may theoretically show up as chronic changes with longer follow-up (92).

Concurrent trastuzumab and new targeted therapies:

Trastuzumab is a humanized monoclonal antibody directed against the growth-factor-receptor Her 2neu, and it is used as adjuvant therapy in BC patients with Her 2neu positive tumours. Halyard and colleagues have studied trastuzumab alone or in combination with RT and they found no increase in skin toxicity or rate of pneumonitis (93).

Bellon *et al* reported an 8 % rate of RP in a small study of 26 patients treated with concurrent trastuzumab and RT (94). A French multicenter study on the potential synergistic effect of concurrent RT and trastuzumab, showed that women who were treated with weekly concurrent trastuzumab and RT developed a decrease of the left ventricular ejection fraction (LVEF) (95).

Pertuzumab, a recombined humanized monoclonal antibody that targets the extracellular dimerization domain for Her2 is not yet used clinically in the adjuvant setting.

Trastuzumab emtansine, T-DM1 monoclonal antibody with the cytotoxic agent emtansine, has been tested for metastatic Her2 neu positive breast cancer, but it is not in clinical use in the adjuvant setting. Both of the latter drugs should be evaluated for added toxicity if they are combined with RT in the future. Other examples of targeted therapies tested in BC are inhibitors of angiogenesis, e.g. bevacizumab and tyrosinkinase inhibitors (TKI). These inhibitors may affect the cardio-vascular function but have not been evaluated in combination with adjuvant RT for BC. Data on TKI-use

obtained from renal cells carcinoma patients indicate a relation with LVEF decline and high-grade hypertension (96).

In conclusion, the addition of targeted drugs to RT must be monitored for potential short- and long-term side-effects (97, 98).

6:4 Summary of literature review

Radiotherapy has been used for over a hundred years. During the last decades, RT-associated late side-effects have been more frequently discussed as the number of long-term survivors increase due to early diagnosis and the introduction of many new effective adjuvant therapies. Thus, both short and long-term effects of RT are becoming increasingly important. The side-effects of RT to lung and heart have been investigated in several randomised and observational studies. These trials have, however, often studied different end-points and the grade of toxicity has not always been reported. Radiotherapy to the IMN is less frequently recommended today and this probably reduces radiation doses both to lung and heart. We need more data on the interaction between clinical co-variates, e.g. cytotoxic treatment and targeted therapies, and post-op radiotherapy, as the clinical practice frequently changes with the introduction of new drugs. Baseline measurements should be gathered before start of any treatment. Results from studies aiming at identifying genetic factors associated with radiosensivity will also be of great value for the clinician.

7. Radiotherapy-related radiological changes with lung with V_{20} lung constraints

7:1 Introduction

Since 1896, one year after Wilhelm Conrad Roentgen's discovery of the X-rays, radiotherapy has been given to very many women with BC (99).

The lung is one of the most radiosensitive and vitally important organs of the body. A report on respiratory side-effects in a patient treated for tuberculosis with irradiation of the thorax was published as early as in 1898. Tyler and Blackman also described clinical and radiographical changes of RT-induced lung damages in 1922 (100).

The temporal distinction between two separate types of radiation-induced lung injury was made as early as in 1925. Today, the development of both pneumonitis and radiation fibrosis is followed in patients who undergo thoracic irradiation where large part of the lungs are irradiated, e.g. in lung or oesophageal cancer patients. The severity of the RT lung injury can for some tumour types vary from a mild cough, dyspnoea, and low-grade fever to severe impairment of the respiratory function.

The risk of acute and chronic side-effects is most importantly influenced by total dose, dose per fraction, and volume of incidentally irradiated lung. Acute radiation pneumonitis occurs after weeks up to 6 months following treatment and may be reversible. One of the earliest clinical reports of this entity was presented by Groover *et al* in 1923 (101). The term radiation pneumonitis was introduced by McIntosh and Spitz in 1939 (102). Ten years later Fried and Goldberg published the first report on late lung tissue response (103). Symptoms of acute radiation pneumonitis can be similar to symptoms of infection or drug-induced pulmonary toxicity. These differential diagnoses most, thus, also be taken into account (104).

RT-induced pneumonitis can also be subclinical and reversible without any sequelae. However, late effects with dyspnoea and impaired daily function months to years after thoracic irradiation can be signs of pulmonary fibrosis. Furthermore, the pulmonary circulation can be affected by severe lung fibrosis and lead to right-sided hypertension and cardiac failure.

7:2 Previously reported outcome data

The incidence of RT-induced lung injury is about 5-15 % in irradiated breast cancer patients, according to Marks (53). Eleven BC studies were reviewed in this publication and the three largest studies included over a thousand patients each (17, 82, 105-113). The rate of pneumonitis varied between 1-19 %. Many of these, reports, however,

originate from the late 1990's when various definitions of CTV and less sophisticated treatment RT-techniques were used. The use of different end-points for lung toxicity in the studies also makes the results difficult to compare. Some studies evaluate clinical symptoms alone and others include radiological methods, e.g. chest X-ray, CT, SPECT, or measurement of respiratory function. Clinical symptoms, e.g. cough and dyspnoea, are often non-specific and can be caused by other factors than RT, e.g. pneumonia, cardiac failure, anaemia, or metastatic disease.

Another obstacle for systemic overviews of RP studies is the lack of consensus on the definition of symptomatic pneumonitis and grading of severity. Furthermore, some studies define RP as an early event and others as a late phenomenon (70).

Our interest in this field originally stems from a clinical observation and a retrospective review of 177 BC women who where treated with RT during 1991-3. We checked the patients' records for notes on a history of respiratory complaints or signs of radiation pneumonitis at the women's pre-scheduled follow-ups 1, 4, and 7 months post-RT. The cases were classified in three groups (no reactions, slight reactions, or moderate reactions impairing daily function and treated with corticosteroids). The old radiotherapy techniques were reconstructed on CT slices of 10 model patients. The percentage of ipsilateral lung volume receiving more than 20 Gy was calculated and V_{20} was 50 % for the treatment technique used after mastectomy (25, 26). About 10-15 % of patients complained of lung symptoms that were recorded as caused by RT.

We therefore continued and prospectively studied short-term pulmonary side-effects following RT in 475 BC patients treated with RT during 1994-8. The incidence of severe post-irradiatory complications among patients treated with loco-regional RT including the IMN was 10 %. Moderate pulmonary complications were rare among women treated with local RT only. The mean irradiated ipsilateral lung volume receiving more than 20 Gy was larger among women diagnosed with clinical and/ or radiological side-effects (25,26). Advanced age and reduced pre-treatment functional level were independently associated with higher rates of post-RT pulmonary complications in our previously followed cohort of BC women.

Based on the outcome data from the above cited and previously published paper, the present studies were conducted with the goal to individualise treatment planning in order to reduce the rate of pulmonary complications (114).

7:3 Summary of Study I

In this part of the intervention study, our aim was to reduce the rates of clinical and radiological pneumonitis by applying a lung dose volume constraint in adjuvant RT for breast cancer.

Patients and methods:

Sixty-six women, who were referred to our Radiotherapy Department for adjuvant RT during 2003-5 were included. They underwent treatment planning aimed at avoiding doses in excess of 20 Gy to more than 30 % of the ipsilateral lung volume, i.e. $V_{20} \leq 30$ %.

Data on potential confounding factors for developing radiation pneumonitis were collected at baseline, e.g. history of pulmonary or cardio-vascular disease, smoking habits, reduced functional level, and pre-RT chemotherapy. Concomitant use of endocrine- or trastuzumab treatment during RT was registered.

The patient's were prospectively followed for symptoms of radiation pneumonitis 1, 4, and 7 months post-RT. Cases of pneumonitis were graded according to modified CTC-criteria (version 2.0) (115).

In each patient, a chest CT was performed 4 months post-RT and the findings were compared to the patient's treatment planning CT.

Computer tomography is based on the X-ray principal: When X-rays pass through the lung they are either absorbed or attenuated at different levels, which creates a matrix or a profile of X-ray beams of different strengths.

New lung abnormalities on post-RT CT at 4 months were analysed with a CT-adapted modification of Arriagada's classification (Fig. 7:1) (116). According to this semi-quantitative classification, the patient's lung should be divided into three regions; apical-lateral (A-L), central-parahilar (C-P), and basal-lateral (B-L).

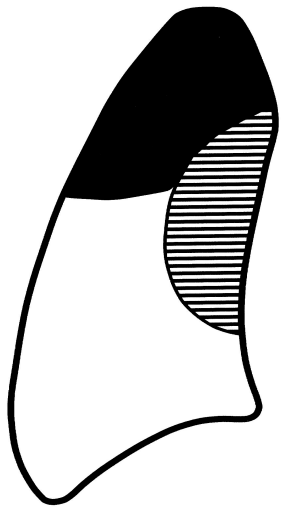

Fig. 7:1. Division of the lung into 3 regions according to Arriagada: apical-lateral (black area), central-parahilar (striped area) and basal-lateral (white area).

Furthermore, increases in density are graded as 0 (no change), 1 (low opacity in linear streaks), 2 (moderate opacity), 3 (complete opacity). The highest density grade of each region is added together. A total score of 1-3 represents a mild radiological reaction, while scores of 4-9 represent moderate to severe reactions.
The individual abnormal lung subvolumes (Fig. 7:2) were contoured and measured and the mean doses were calculated.

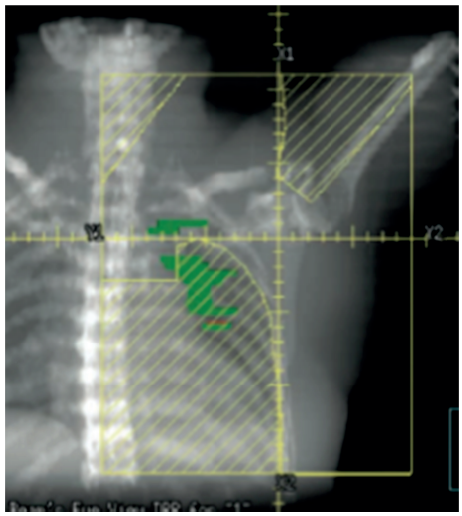

Fig. 7:2. Frontal image (Beam's eye-view) depicting the position of the frontal photon beam covering the supraclavicular fossa and axilla. Green areas represent regions with density changes.

Results:

Short-term symptomatic radiation pneumonitis was very rare in this treatment series, i.e. one grade 2 (moderate) and three grade 1 (mild). The ipsilateral V_{20} was higher in the symptomatic women than in asymptomatic cases, i.e. 29 % vs 24 % (p=0.04).

The majority of patients developed mild radiological changes on the post-RT CT (total scores 1-3), but these findings were in most cases not accompanied with respiratory symptoms. The affected lung volumes were typically small, i.e. mean volume 20 ml, and the average dose was high, i.e. 37 Gy, which was significantly higher than the average ipsilateral mean lung dose of 13 Gy.

The relation between radiological changes and patient/therapy specific factors were tested with uni- and multivariate analyses. Fewer cases of moderate-severe radiological changes were seen in younger patients and in patients undergoing pre-RT chemotherapy according to univariate analyses. Four different multivariate models were tested which each included the studied dosimetric factors separately, i.e. V_{13}, V_{20}, V_{30}, and MLD, and the factor age and pre-RT chemotherapy. None of the models attained a statistical significance, but there was a trend for a relation between V_{30} and density changes of 4-9 (p=0.08).

There was a strong interrelation among all the studied dosimetric factors.

Discussion:

Modern radiation treatment planning aimed at minimizing the incidentally irradiated lung volume resulted in few cases of short-term lung symptoms. The average ipsilateral V_{20}-value in symptomatic women, i.e. 29 % was higher than in asymptomatic cases. The majority of cases developed mild radiological changes on CT, but these were, however, generally not accompanied by symptoms. It may be warranted to follow these mild abnormalities a later time point to rule out the development of chronic symptoms.

7:4 Summary of Study II

Patients and methods:

In this part of our project, 88 women with BC who had undergone post-operative RT with a lung dose volume constraint, i.e. ipsilateral $V_{20} \leq 30$ %, were evaluated for changes on chest X–ray (Fig. 7: 3) and effects on Quality of Life (QoL) 4-5 months after treatment. The post-RT radiological changes were compared with the outcome in our previous trial of 137 irradiated women when a pre-planned lung dose-volume constraint was not used (27,28). Furthermore, the outcome on chest X-ray exams in the present series was compared to findings on chest CT. The semi-quantitative Arriagada classification was used for the analysis of radiological changes, which takes into account number of affected lung regions and highest grade of density increase (116).

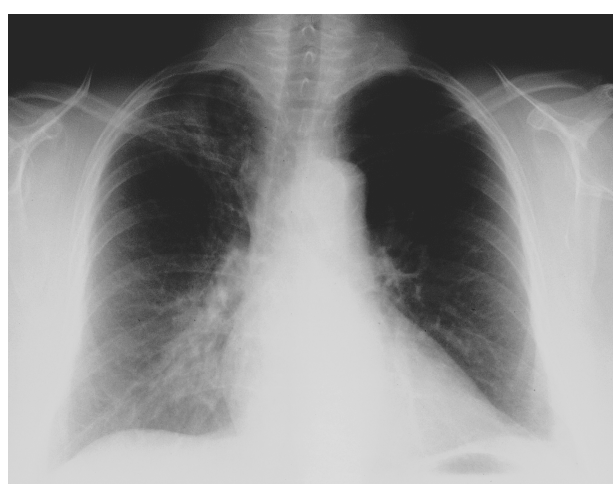

Fig. 7:3. Example of grade 2 abnormalities in all 3 regions of the right lung on chest X-ray.

To study effects on QoL we used the European Organisation for Research and Treatment of Cancer (EORTC) form QLQ-30 and the EORTC QLQ-BR-23 (117, 118). The patient filled out the forms prior to and 4 months after RT. We selected to analyse items related to pulmonary symptoms such as physical functioning, role functioning, social functioning, fatigue, pain, dyspnoea, insomnia, and future perspective. A high score on the global health status/functional scale represent a high/ healthy level of function. In contrast, a high score on the symptom scale reflects a high level of symptoms/ problems.

Result:

Only one patient developed moderate lung symptoms, which were treated with corticosteroids, whereas six patients were diagnosed with mild symptomatic radiation pneumonitis. No relation was found between symptomatic and radiological RP on chest X-ray or CT in this series. There was a significant reduction of moderate-severe radiological RP on X-ray for the treatment technique LRRT+IMN compared to our earlier trial ($p<0.001$). However, there was no difference between the old and present series for the treatment technique where the IMN were excluded. We found no correlation between any dosimetric factors or the studied co-variates and radiological changes on chest X-ray in multivariate analysis. In the present series, there was no agreement between X-ray and CT as diagnostic tools for radiological RP, which probably was due to the small lung volumes that were affected.

Chest CT was, thus, a more sensitive method to detect small affected lung volumes compared with X-ray. The dosimetric factor V_{13} was most strongly and independently related with radiological changes on CT. Quality of Life was very little affected by RT in this treatment series. Due to pre-RT chemotherapy the patients started with high scores of fatigue. Role functioning, social functioning, and future perspective were improved 4 months after RT compared to baseline.

Patients treated with high V_{13} appeared, however, not to recover equally well, e.g. difficulties to take short walks, and this association was also reported when the patient rated their overall total QoL during the last week. Furthermore, there was no effect of RT on physical functioning, pain, or dyspnoea in this series.

Discussion:

The results of this study indicate that the used dose volume constraints significantly reduced moderate-severe radiological RT on chest X-ray compared to our previous study. The lung changes could not always be detected on chest X-ray and were also less frequent and limited on chest CT. Ipsilateral V_{13} was correlated with occurrence of

radiological RP on CT. Co-variates such as smoking, age, chemotherapy, endocrine - or trastuzumab therapy did not influence this outcome. There were, however, few events in this study, which hampers its ability to detect small-moderate statistical relations.

8. Radiotherapy-related changes in pulmonary function with V_{20} lung constraints

8:1 Introduction

Pulmonary function tests (PFTs) must be performed under standardized conditions (119). The tests are dependent on the patient co-operation. The methods are inexpensive, reproducible, and widely available. The most common used measurements are vital capacity (VC); the maximum volume of air that can be expired after maximum inspiration, forced expiratory volume in 1 second (FEV1); the volume of air exhaled during the first second of a forced expiration manoeuvre is started from the level of total lung capacity, diffusing capacity of carbon monoxide (DLCO); the ability of gas to diffuse across the alveolar-capillary membranes.

8:2 Previously reported outcome data

Our previous study evaluated PFTs 5 months after RT that did not include a lung dose volume constraint in 144 women with BC in comparison to a pre-RT examination. Patients treated with LRRT experienced a mean reduction of both DLCO and VC. In the 9 % of women who developed moderate symptomatic pneumonitis there was a significantly larger mean paired reductions in VC than in asymptomatic patients (29). Surprisingly, there was a mean increase in diffusions capacity by 7 % ($p=0.004$) following RT that probably was due to transient toxicity of the chemotherapy that had been administered prior to RT.

Vernbanck *et al* have studied small airways in BC patients before and after RT to examine whether the function are normal at baseline before RT (120). The study group consisted of non-smoking, middle age women with no history of respiratory disease. They were compared with healthy controls and were found to have normal values before RT.

Jaén and co-workers reported data on short-term and long-term changes in pulmonary function after LRRT in 39 women with follow-up after 6, 12, and 36 months. All PFTs decreased at 6 months, however, all except DLCO returned partially to pre-treatment values after 12 months (121). Longer follow-up for 7 years showed a decrease in the first 2 years but recovery to baseline values in the long-term. The diffusion capacity was reduced for 24 months before returning to normal. This study also looked at changes in perfusion and ventilation scintigraphy data that showed a similar pattern as for the DLCO abnormalities (122).

8:3 Summary of Study III

Patients and methods:

In this study we investigated changes in PFTs and short-term symptomatic radiation pneumonitis (RP) in 64 women. Their mean age was 55 years. The ipsilateral lung dose volume constraint V_{20} < 30 % was applied in the treatment planning. Data on potential confounding factors for pulmonary complication were collected prospectively as previously described. The study population had no major medical conditions and good functional levels at baseline.

Patients were monitored 1, 4, and 7 months after RT for respiratory symptoms. Pulmonary function tests were performed before and 5 months after completion of treatment.

Chemotherapy was concluded 3-4 weeks before RT. The most common regime consisted of FEC (5-fluorouracil 600 mg/m^2, epirubicin 60-75 mg/m^2, and cyclophosphamide 600 mg/m^2, d 1q 3 weeks x 6). Concurrent chemotherapy was never given. The outcome was compared with our previous treatment series (29).

Result:

In a few cases we had to accept a somewhat higher V_{20} than 30 % due to the patients' anatomy. There was, however, a statistical significant reduction in mean V_{20} (35 % vs. 26 %) and V_{30} (24 % vs. 16 %) compared with our previous trial. We found four mild and one moderate cases of symptomatic RP, which was a lower frequency than in our previous report ($p<0.001$). The mean changes in VC and DLCO appeared lower than in our previous report in which constraints was not used.

We found no correlation between the evaluated co-variates and PFTs changes, i.e. DLCO and VC, except for pre-RT chemotherapy and less post-RT DLCO changes. Again, this was probably influenced by low baseline DLCO-values after chemotherapy prior to start of RT, as cyclophosphamide is known to induce local inflammation in the lung parenchyma (88).

Tamoxifen is reported to influence the risk for post-RT fibrosis (91). We have previously reported that concomitant tamoxifen during RT has no influence on VC and DLCO changes (29). However, when we now re-analysed the data for women who received LRRT including the IMN in our earlier study and included individual dosimetric data we found a possible relation between tamoxifen and VC-changes.

Discussion:

Radiation pneumonitis was rare when lung dose volume constraints and 3-D planning were used. The lack of relation between dosimetric factors and reduction in PFTs in

this present trial may be due to the limited study size. Another cause could be the observed small mean changes in VC and DLCO with the used lung dose volume constraints. Ideally, PFTs should be performed before start of any BC therapy, as the diffusion capacity of the lung is affected by chemotherapy. In this study, the most commonly used chemotherapy was FEC. Both cychlophoshamide and methotrexate are known to cause pulmonary toxicity by local inflammation. In the re-analysis of our earlier cohort of 144 patients with the inclusion of individual dosimetry data, tamoxifen intake appeared to increase post-RT VC-changes.

8:4 Other techniques for functional studies

Single photon emission computed tomography (SPECT) is used to map organ function and metabolism. The combination of CT and SPECT can show the exact localization of non-functioning tissue and it is a very sensitive method for monitoring radiation lung damage (123-127).

Ma and colleagues investigated the association between RT-induced changes in lung tissue density and global function in lung, lymphoma, and breast cancer patients. They found a weak quantitative association between the degree of increase in lung density as defined by CT and the percentage reduction in PFTs (128). They also included SPECT in their study with the belief that SPECT imaging would provide a more physiological assessment of the lung function than CT alone.

9. Radiotherapy-related long-term functional and radiological pulmonary changes

9:1 Introduction

Radiotherapy is known to cause late lung side-effects and from 6-8 months after RT fibrosis may develop.

There are relatively few reports on the long-term consequences of RT on the respiratory function in BC patients (122,129-133). Some of the most important earlier publications are listed in Table 2 of Paper IV.

A few of these reports suggest that lung function changes after irradiation for BC follows a biphasic pattern. This consist of an early reaction with a maximum after six months and partial recovery after one year followed by a late progressive worsening after 8-10 years.

The purpose of Study IV was to assess late pulmonary side-effects in women irradiated with LRRT without a pre-planned lung dose volume constraint at our Department between 1994-8, and to compare their present lung function with the their pre-RT respiratory status.

9:2 Summary of Study IV

Patients and methods:

We re-examined women from our earlier cohort of 475 patients with Stage I to Stage II node positive BC referred to the Radiotherapy Department at Stockholm Söder Hospital for adjuvant RT during 1994-8. Computer tomography was performed in 70 of these women after a median of 11 years after RT. Twenty-nine of the women had undergone the pre-RT, the 4 months post-RT, and the late chest CT examinations. Fifty-six women performed the long-term repeated PFTs follow-up.

Data on potential pre-disposing factors for RP, i.e. history of cardiovascular- or pulmonary co- morbidity, smoking habits, and reduced functional level, were collected both before start of RT and at the long-term follow-up. To evaluate the radiological lung changes on CT we used the previously described semi-quantitative CT-adaption of the Arriagada classification (116).

Results:

The long-term follow-up showed a 10-15 % reduction of the median matched VC, TLC, and FEV1 measurements compared to pre-RT levels. Measurements of DLCO increased after 11 years, which was probably due to a transient effect of pre-RT chemotherapy. The median matched percentage of the predicted DLCO value at 11

years was, however, only 86 %, which suggests a chronic therapy-induced reduction also of this metric. Changes on CT visible at 4 months after RT were still detected after 11 years and appeared similar at this follow-up. We found a correlation between V_{20} and long-term CT-changes but not with VC-changes.

Discussion:

Similar lung abnormalities on CT as after 4 months post-RT were detected at a follow-up after 11 years. The median percentage of the predicted VC, FEV1, and TLC were lowered 10-15 %. Most of the women received adjuvant chemotherapy pre-RT. It would have been of interest to measure the baseline values before start of adjuvant chemotherapy as this affected the pre-RT DLCO results. Fibrosis is an on-going process according to some researcher. To follow this cohort of women for additional years would perhaps answer the question if the lung changes will diminish or increase with time.

10. Radiotherapy-related heart disease

10:1 Introduction

There are many pieces of evidence in the literature that RT may be cause late morbidity to the heart (23, 134-139).

The law of Bergonie and Tribondeau was developed in 1906 by two French radiobiologists.

It states that the radiosensitivity of cells is directly proportional to their reproductive activity and inversely proportional to their degree of differentiation. According to this hypothesis, the heart is considered to be a radioresistant organ. In 1957, Pearson, however, reported that intimal proliferation secondary to chest wall irradiation might have caused myocardial infarction in two women (140). As more case reports followed, Fajardo and Stewart started experimental studies in this field in the late 1960's. These studies showed that the heart and vessels are sensitive to RT (141). High incidences of coronary artery disease were also observed in patients who as children or adolescents were irradiated during 1960-1991 for Hodgkin's disease (142). Furthermore, irradiated heart volume and dose to heart are related with an increased risk of death due to ischaemic heart disease in patients treated for Hodgkin's disease according to Eriksson *et al* (143). Cusack's overview, which was published 1987 and updated 1994, demonstrated an excess of cardiac deaths among women irradiated for BC compared with women only treated with surgery (5,144). A study of 55,000 women diagnosed with BC in Sweden during 1970-85 showed an increased risk of death from myocardial infarction among women with cancer of the left breast compared to the right side (145). An updated analysis of this study in 2003, with women diagnosed until 1996 and including 90,000 cases, found that the mortality ratio, left vs right (146), for all cardiovascular diseases was 1.04 (95 % CI: 1.00-1.09).

A number of large randomised trials have shown increased risk of cardiac mortality after BC irradiation (6,147). Even the effect of low doses of environmental and occupational radiation exposures have been studied and shown to increase the risk for myocardial infarction (148, 149).

More than 30 different breast cancer RT regimes have been used in Sweden since the 1950's. Cardiac doses varied between < 1 Gy to 24 Gy for the heart and between < 1 Gy to 46 Gy for the LAD coronary artery (150). The different anatomical structures in the heart may have different radiation tolerances (151,152). Increased knowledge on

the dose-response relationship for the development of ischaemic heart disease would be of great importance in BC RT-planning.

10:2 Summary of Study V

Patients and methods:

A population-based case-control study was conducted in Denmark and Sweden with women treated with external RT for invasive BC during 1958-2001. In Sweden, women younger than 70 years and living in Stockholm were considered for the study. Major coronary events were defined as the diagnosis of myocardial infarction according to the International Classification of Diseases, 10 th Revision (ICD-10 codes 121-124); coronary revascularization, or death from ischemic heart disease (ICD-10 codes 120-125). Events of angina alone were not included. Women without a histological diagnosis of BC were excluded. Other exclusion criteria were previous cancer (apart from non-melanoma skin cancer) and previous RT to the thoracic area. All other women who received RT were cross-matched with the nationwide registries of diagnosis at time of hospital discharge and cause of death. Ninehundred and sixty-three cases and 1,205 controls were included in the analysis.

Data on the medical history at time of BC diagnosis and treatment of BC were abstracted from hospital oncology records. Each individual RT-chart including photographies of treatment fields and dose-plans were copied. Virtual simulation and planning based on CT (for a few regimes manual planning) were used to reconstruct each RT-regime on the CT of a woman with a typical anatomy (150,153). Dose volume histograms were calculated for the whole heart and for the left anterior descending coronary artery for the different regimes. Equivalent dose in 2 Gy fractions (EDQD2) was calculated from the dose volume histograms (21):

$$nd((d+ \alpha/\beta)\div(2+ \alpha/\beta))$$

n=number of fractions

d=dose to the heart per fraction (in Gy)

α/β: 2

Event rate ratios (RR) were estimated using conditional logistic regression with stratifications for each matching factor.

Results:

Women irradiated for left-sided tumours had higher rates of major coronary events than women undergoing irradiation for right-sided cancers (p=0.002). There were,

however, no other strong relations between this end-point and tumour characteristics or additional cancer treatments apart from a borderline significant association with a positive nodal status (RR: 1.20; p=0.06).

In contrast, the overall RR for a major coronary event in women with a history of ischaemic heart disease compared with cases without this co-morbidity was 6.7. The event rate ratio was 13 during the first 10 years after cancer diagnosis and 2.1 during later years (p<0.001). Elevated RRs were also associated with a history of other circulatory diseases, diabetes, or chronic obstructive pulmonary disease, and smoking and high body-mass index, or history of regular analgesic use. The event rate ratio for the presence of one or several of these factors but no ischaemic heart disease was 1.96 overall; 2.6 during the first 10 years compared with 1.6 during later follow-up (p=0.03). The overall average estimated mean dose to the entire heart was 4.9 Gy (range from 0.03 to 27.72). Mean dose to the heart was 6.6 Gy for women irradiated for left-sided tumours compared to 2.9 Gy for cases with right-sided cancers. The rate of major coronary event increased by 7.4 % for each increase of 1 Gy in mean radiation dose delivered to the heart (p<0.001) (Fig. 10:1). Furthermore, the relation between the percentage increase/ Gy in the rate of major coronary events and number of years after RT was studied. The risk increase started in the first 5 years after exposure, without any apparent threshold, and was evident for at least 20 years (see Table 3 Paper V).

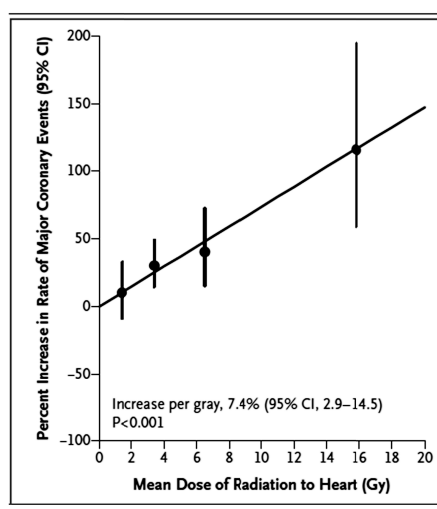

Fig. 10:1. Major coronary events and mean heart dose as compared with estimated rate with no radiation exposure.

The results of these analyses were unchanged when data on potential confounding factors were included, e.g. age at diagnosis of BC and present of cardiac co-morbidity.
The mean doses to the left anterior descending coronary artery (LAD) and to the entire heart were also estimated and compared and they were related (correlation coefficient 0.76). The estimated mean dose of irradiation to the heart was a better predictor of major coronary events than the estimated mean dose to the LAD according to multivariate modelling ($p<0.001$).
To validate our data on estimations of absolute risks, the result from this case-control study was combined with data on rates of death from ischaemic heart disease for the 15 most western countries of the European Union combined (Fig. 10:2).

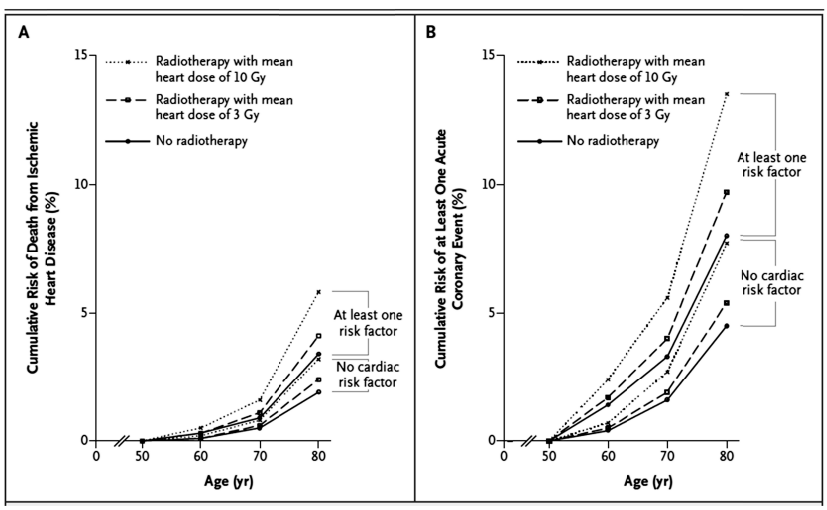

Fig. 10:2. Cumulative risks of death from ischaemic heart disease and at least one acute event.

The resulting baseline lifetime risk estimates were similar to recently reported data from the US.
For example, in a 50-year old woman with no pre-existing cardiac risk factors, irradiation with a mean dose to the heart of 3 Gy would increase her risk of death from ischaemic heart disease before age 80 from 1.9 to 2.4 %. It would increase her risk of experiencing at least one acute coronary event from 4.5 to 5.4%. If the average heart dose was 10 Gy, the risk of death from ischaemic heart disease would increase from 1.9 to 3.4 %, and the absolute risk of one or more coronary events would increase by

3.2 percentage points. For women with one or several pre-existing cardiac risk factors both the risk at baseline and the absolute increase in risk are elevated.

Discussion:

We found that rates of major coronary events increased linearly, without a threshold, with incidental irradiation of the heart by 7.4 % per Gy. The percentage increases per unit were similar for women with or without pre-existing cardiac risk variables, which suggests that the absolute increases in risk for a certain dose to the heart were larger for woman with pre-existing risk factors.

Almost all of the women in this study were treated before 3-D planning was in use. Furthermore, few of the women were younger than 40 years of age at the time of treatment and caution is therefore needed when applying our results on this younger age group.

In our cohort, there were also few women treated with antracyclines, taxanes, or targeted therapies, which all are known to affect the heart by themselves.

Our results point out the importance for the use of RT-techniques where the heart is excluded from the radiation fields. It is therefore important to outline both the heart and the coronary arteries as OAR in the dose planning process and to minimize doses to these volumes. It is also necessary to weigh the pros and cons for the individual patient when adjuvant therapies are selected.

Today, there are alternative RT-methods available which reduce the incidental dose to the heart. Respiratory gating delivers the radiation in the breathing phase when the heart is out of the radiation field (154,155). The patient can also be treated in a prone position (156-158). Some centres have used Intensity Modulated Radiation Therapy, IMRT, to lower dose to the heart. The latter technique may lower the dose to the heart but it involves more radiation fields and larger volumes of normal tissue are therefore exposed to low dose radiation (159,160). Proton therapy is another alternative technique for lowering dose to heart, but no randomised study has yet been performed with this modality in BC (161,162).

11. Conclusion of Studies

Study I

Adjuvant BC with modern treatment planning and the incorporation of an ipsilateral lung dose volume constraint of V_{20} < 30 % resulted in few cases of short-term symptomatic radiation pneumonitis. The ipsilateral V_{20} was higher in symptomatic compared to asymptomatic women, 29 % vs. 24 % (p=0.04). The majority of cases developed, however, mild radiological changes on chest CT. There was a trend for relation between V_{30} and moderate-severe density changes on chest CT (p=0.08). The mean dose in lung subvolumes with radiological density abnormalities in affected patients was 37 Gy (SEM: 1.5). This was significantly higher than the average ipsilateral MLD of 13 Gy (p=0.001). The analyses of the relation between the different dosimetric factors, i.e. ipsilateral V_{13}, V_{20}, $V_{30,}$ and MLD, and other co-variates and the studied end-points with multivariate modelling were hampered by the study sample size and relatively few events.

Study II

Adjuvant BC RT with modern treatment planning and the incorporation of an ipsilateral lung dose volume constraint of $V_{20} \leq 30$ % resulted in fewer cases of short-term radiological changes on chest X-ray compared with our previous study. There was also a statistically significant reduction in average V_{20} (35 % vs. 26 %) and V_{30} (24 % vs. 16 %) in the present series compared with our earlier trial. The lung changes in the present trial could not always be detected on chest X-ray and they were also more infrequent and limited on chest CT than in our previous reports. There was no agreement between X-ray and CT as a diagnostic tool for radiological pneumonitis. There was, furthermore, no relation between symptomatic and radiological RP on chest X-ray or CT in the current series, which can be due to the very few symptomatic cases. Ipsilateral V_{13} was most strongly an independently related with mild-severe radiological changes on CT. Thus, chest CT was a more sensitive method to detect small affected volumes than X-ray.

Also Quality of Life was very little affected by RT in the present cohort of irradiated BC women. Due to pre-RT chemotherapy, the patients started with higher scores of fatigue. Role functioning, social functioning, and future perspective were improved 4 months after RT compared to baseline values. Patients treated with high V_{13} appeared, however, not to recover equally well.

Study III

The effect of adjuvant BC RT with modern treatment planning and the incorporation of an ipsilateral lung dose volume constraints of $V_{20} \leq 30$ % on short-term pulmonary function was analysed in this report and compared with an earlier treatment series in which a constraint was not used. The mean changes in VC (-0.11 L vs. -0.15 L) and DLCO (-0.20 mmol/kPa min vs. -0.39 mmol/kPa min) appeared lower than in our previous series. We found no relation between the studied dosimetric factors nor co-variates and PFTs changes, except for pre-RT chemotherapy and less post-RT DLCO reduction. This was probably influenced by the administration of chemotherapy before start of RT. In future trials, base line PFTs should be performed before start of any therapy.

Study IV

This study was a long-term follow-up of pulmonary side-effects in adjuvant BC RT without lung dose volume constraints in our previously studied cohort of patients. Regional CT abnormalities and PFTs changes found 4 months after RT were still detected after a median follow-up of 11 years. There was a statistical correlation between V_{20} and CT-scoring but no statistical correlation between V_{20} and VC-changes. As the magnitude of the chronic VC-decline, -15 %, and the radiological abnormalities could be of clinical importance it is of value to pursuit to reduce the volume of incidentally irradiated lung.

Study V

This study evaluated the long-term cardiac effect of radiation exposure in women treated with RT for BC. The rates of major coronary events increased linearly with the mean dose to the heart by 7.4 % per Gy, without any apparent threshold. The risk started within 5 years after RT and continued into the third decade after treatment. The proportional increase in the rate per Gy was similar in woman with and without cardiac risk factors at the time for treatment. Thus, women with pre-existing cardiac risk factors had a greater absolute risk from radiotherapy than other women.

12. Future perspectives

Radiotherapy after BC surgery reduces local recurrences and prolongs breast cancer specific survival. However, studies have also shown that women treated for more than three decades ago still experience late side-effects. Longer follow-up of the more recent large studies, which included modern RT-techniques, will likely show reduced doses to the heart and lung and fewer side-effects. However, we do not have enough knowledge on the long-term effects from the new, potentially lung- and cardio-toxic, systemic therapies. It is therefore of great value to continue monitoring BC patients undergoing combination therapy with respect to cardio-pulmonary side-effects and to identify genetic factors associated with radiosensitivity. Patients with BC should be informed about the benefits and potential risks with RT as well as the risk of smoking. Risk factors for heart disease, e.g. hypertension, high cholesterol levels, and diabetes, should be identified and treated. It is also of importance to further develop and implement the new RT-techniques, e.g. respiratory gating and active breathing control, to lower incidental dose to the heart. In some selected cases partial breast irradiation could be an option but this, however, requires good surgical margins and negative axillary lymph nodes. The present work on national guidelines for target delineation and the construction of a cross sectional atlas for CTV and PTV in BC is also of importance.

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