Long-Term Symptoms after Breast Cancer Radiotherapy

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To my family

Linnea, Emilia, Olivia, and Magdalena

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Abstract

Since breast cancer is the most common cancer among women worldwide and the relative 10-years overall survival is 80% there is an increasing number of women living with a history of breast cancer treatment. This results in a great number of women in the society having received breast cancer radiotherapy. The purpose of this study was to identify and quantify self-reported long-term symptoms/side-effects caused by irradiation and correlate these to patient and treatment related risk factors. Furthermore, we wanted to investigate how the dose-volume distribution of ionizing radiation delivered to a certain anatomical volume contributed to the occurrence of certain symptoms, i.e. a dose-volume response analysis.

We interviewed women that were treated with breast cancer surgery and postoperative radiotherapy up to 20 years earlier; based on these interviews we made a questionnaire. The questionnaire was sent to two different cohorts of women having had breast cancer treatment three to 17 years earlier. Cohort 1: 422 women who were randomised between 1991 and 1997 to receive adjuvant tangential breast irradiation or not after breast conserving surgery with axillary dissection. Cohort 2: 1091 women who had adjuvant breast cancer radiotherapy based on a 3D-dose plan between 1999 and 2004 at Sahlgrenska University Hospital, Gothenburg.

Paper I: Based on cohort 1 we found that 8.8% of the women having undergone radiotherapy and surgery reported weekly breast pain versus 0.6% of the women with surgery alone (RR 15.1 95% CI 2.03-112). Significantly increased occurrence after radiotherapy was also observed for disturbances of skin sensation. Daily life and analgesic use did not differ between the groups. Paper II: Our next step was to identify risk factors that contributed to breast

pain after breast cancer radiotherapy (cohort 1 and 2). Higher age at treatment (RR 0.96; 95% CI 0.94-0.98, annual decrease) and longer time since treatment (RR 0.93; 95% CI 0.88-0.98, annual decrease) were related to a lower occurrence of breast pain. For example among women up to 39 years of age at treatment, 23.1% had breast pain, compared with 8.7% among women older than 60 years (RR 2.66; 95% CI 1.33-5.36). In paper III and IV we reported long-term symptoms after radiotherapy including the regional lymph nodes, i.e. irradiation of the plexus brachialis, or not (cohort 2). We found that paraesthesia in the hand was reported by 20% after regional radiotherapy compared to 13% without regional radiotherapy (RR 1.47; 95% CI 1.02-2.11). RR adjusted for oedema in the hand (RR 1.28; 95% CI 0.93-1.76). Among the women who received irradiation $\geq$40 Gy to a volume of >13.5 cm^3 of the brachial plexus 25% reported paraesthesia, RR 1.83 (95% CI 1.13-2.95). The risk was still significant after adjustment for oedema (RR 1.64; 95% CI 1.12-2.41).

Conclusions: Radiotherapy after breast-conserving surgery among women treated for breast cancer increases the occurrence of breast pain, especially among younger women. Furthermore, regional radiotherapy increases the occurrence of paraesthesia in the hand and our results indicate that there seems to be a correlation between larger irradiated brachial nerve volumes and an increased risk of reporting paraesthesia.

Keywords: Radiotherapy, breast cancer, long-term symptoms, breast pain, supra clavicular, plexus brachialis.

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Sammanfattning på svenska

Bröstcancer är den vanligaste formen av cancer bland kvinnor, och i Sverige kommer var tionde kvinna att få bröstcancer under sin livstid. Långtidsresultaten för hela bröstcancergruppen är goda med en relativ tio års överlevnad kring 80 procent. Detta innebär att vi har en växande grupp av ”canceröverlevare” vilka kommer att leva under många år med eventuella behandlingsrelaterade biverkningar från exempelvis kirurgi, kemoterapi och strålbehandling. Vi vet att tillägget av strålbehandling efter bröstcancerkirurgi minskar återfallsrisken vilket i sin tur leder till en förlängd överlevnad. Metaanalyser visar att för vart fjärde lokalrecidiv som undviks med strålbehandling så räddas en kvinna från att dö i bröstcancer.

Detta arbete syftar till att identifiera och kvantifiera självrapporterade bestående strålrelaterade symtom av en modern strålbehandlingsteknik samt att söka efter patient- och behandlingsrelaterade riskfaktorer. Vidare att studera hur förekomst av symtom på lång sikt varierar med dos inom specifika anatomiska områden.

Vi hade som mål att skapa ett frågeformulär (så heltäckande som möjligt) som byggde på patientens egna upplevelser ur vardagen flera år efter avslutad behandling. Vi utvecklade ett formulär som var baserat på semistrukturerade djupintervjuer med kvinnor som behandlats för bröstcancer 3 till 20 år tidigare. Nya intervjuer genomfördes fram tills inga ytterligare symtom togs upp av de intervjuade kvinnorna (symtommättnad). Totalt intervjuades 22 kvinnor vilka alla hade behandlats med olika former av kirurgi och strålbehandling. Utifrån deras angivna symtom utformades ett omfattande frågeformulär (80 sidor). Frågorna i formuläret ansiktsvaliderades sedan med kvinnor som genomgått bröstcancerbehandling för att vi skulle försäkra oss om att frågorna förstods på det sätt vi tänkt oss och därmed passa till den grupp av kvinnor som skulle ingå i studien. En pilotstudie genomfördes därefter för att bedöma vilken svarsfrekvens som kvinnor i denna grupp har för formuläret och ifall någon specifik fråga skulle bli obesvarad. Vi fortsatte med huvudstudien när 30 av 32 formulär besvarats.

Under 2007och 2008 tog vi kontakt med och skickade formulär till två olika grupper av återfallsfria bröstcancerbehandlade kvinnor. Kravet på återfallsfrihet var för att vi inte skulle blanda samman symtom av sjukdom med symtom relaterade till behandling.

Patientgrupp 1: För att kunna urskilja strålorsakade symtom från kirurgiorsakade symtom skickade vi under 2007 enkäten till kvinnor (antal 422 st) som varit med i en svensk randomiserad studie, SweBCG91-RT, mellan åren 1991 och 1997, dvs. 10 till 17 år tidigare. Kvinnorna hade

genomgått sektorresektion och axillutrymning p.g.a. lokaliserad bröstcancer mindre än 5 cm och utan lymfkörtelspridning. De randomiserades till tangentiell strålbehandling av bröstet eller ingen ytterligare behandling.

Patientgrupp 2: Under 1999 blev det standard med 3D-dosplanering på Jubileumskliniken, Sahlgrenska Universitetssjukhuset i Göteborg för alla kvinnor med bröstcancer. Under 2008 kontaktade vi kvinnor som fortlöpande blivit strålbehandlade på Jubileumskliniken, Sahlgrenska Universitetssjukhuset under perioden 1999 tom 2004, dvs. 3 till 9 år tidigare (antal 1091 st). Syftet med denna grupp var att få beskrivit symtomen från kvinnor som fått en mer varierad, modern och avancerad strålbehandling samt där även dessa kvinnors 3D-dosplaner fanns tillgängliga för att mer specifikt studera dosens betydelse inom olika volymer för uppkomsten av symtom.

Resultat:

I *artikel 1* jämför vi symtom efter bröstbevarande kirurgi och strålbehandling med symtom efter bröstbevarande kirurgi enbart. Vi fann att kvinnor som fått strålbehandling rapporterade ömhet i bröstet oftare, 8.8%, i jämförelse med de kvinnor som inte fått strålbehandling, 0.6%. Vidare fann vi en ökad förekomst av känselstörningar i huden efter strålbehandling. Det fanns dock ingen skillnad gällande konsumtionen av smärtstillande tabletter eller välbefinnande mellan grupperna. Syftet med *artikel 2* var att finna riskfaktorer bakom bröstömhet 3 – 17 år efter bröstbevarande kirurgi och strålbehandling av bröstet. Åldern visade sig vara den viktigaste faktorn. Förekomsten av bröstömhet var 9 % i gruppen över 60 år, 12 % i gruppen 50 – 59 år, 21 % i gruppen 40 – 49 år och 23 % bland kvinnorna yngre än 40 år. Kort tid sedan behandling var också relaterat till en högre förekomst av bröstömhet, förekomsten av bröstömhet var 16 % i gruppen som hade behandlats för 3 – 5 år sedan, 13 % efter 6 – 9 år och 9 % efter 10 – 17 år. I *artikel 3* jämför vi symtom i hand/arm med eller utan regional lymfkörtel strålbehandling. Denna strålbehandling ger också dos till plexus brachialis (armens känsel- och motoriknerv). Efter axillkirurgi och regional strålbehandling rapporterade 20 % stickningar i handen i jämförelse med 13 % utan strålbehandling. Förekomsten av svullnad i handen var 22 % efter strålbehandling jämfört med 15 % utan strålbehandling. Om man justerar stickningarna för svullnad försvinner den säkerställda skillnaden, d.v.s. det kan också vara svullnaden som indirekt orsakar stickningarna i tillägg till en direkt strålpåverkan av nerven. I *artikel 4* fann vi att bland de kvinnorna som fått en stråldos av minst 40.0 Gy till en stor volym ($\geq$13.5 cm^3) av plexus brachialis rapporterade 25 % stickningar i jämförelse med 13 % utan strålbehandling. Även efter justering för svullnad kvarstår stor bestrålad volym som en riskfaktor för stickningar i handen vilket tyder på en direkt strålpåverkan av nerven.

Slutsatser:

Resultaten av våra studier tyder på att: Postoperativ strålbehandling av bröstet, i tillägg till bröstbevarande kirurgi, leder till en ökad förekomst av ömhet i bröstet. Störst risk för bröstömhet har de yngre kvinnorna. Strålbehandling av de regionala lymfkörtlarna leder till en ökad förekomst av stickningar i handen. Dessutom att det finns en relation mellan dos till plexus brachialis och stickningar i handen.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Lundstedt D, Gustafsson M, Malmström P, Johansson K-A, Alsadius D, Sundberg A, Wilderäng U, Holmberg E, Anderson H, Steineck G, Karlsson P. Symptoms 10-17 years after breast cancer radiotherapy data from the randomised SWEBCG91-RT trial.
Radiotherapy & Oncology 2010; 97(2):281-7.

II. Lundstedt D, Gustafsson M, Steineck G, Malmström P, Alsadius D, Sundberg A, Wilderäng U, Holmberg E, Johansson K-A, Karlsson P. Risk factors of developing long-lasting breast pain after breast cancer radiotherapy.
Int J Radiat Oncol Biol Phys. Epub 2011 Nov 11.

III. Lundstedt D, Gustafsson M, Steineck G, Johansson K-A, Alsadius D, Sundberg A, Wilderäng U, Holmberg E, Karlsson P. Long-term symptoms after radiotherapy of supraclavicular lymph nodes in breast cancer patients.
Radiotherapy & Oncology Epub 2012 Feb 7.

IV. Lundstedt D, Gustafsson M, Steineck G, Johansson K-A, Alsadius D, Sundberg A, Wilderäng U, Holmberg E, Karlsson P. Dose-volume analysis of radiotherapy to the plexus brachialis in breast cancer patients.
Manuscript

Content

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
APBI	Accelerated Partial Breast Irradiation
ALND	Axillary Lymph Node Dissection
BCS	Breast-Conserving Surgery
BMI	Body Mass Index, kg/m^2
BPN	Brachial Plexus Neuropahy
CMF	Cyclophosphamide, Methotrexate, and 5-fluorouracil
CI	Confidence Interval
CT	Computed Tomography
DVH	Dose Volume Histogram
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ER	Estrogen Receptor
EQD_{2Gy}	Equalized total dose in 2 Gy/fraction
FAC/FEC	5-fluorouracil, anthracyclin (epirubicin/doxorubicin), and cyclophosphamide
Gy	Gray, the SI unit for absorbed radiation dose (1 Gy = 1 Joule/kg)
IMRT	Intensity-Modulated Radiation Therapy
ITT	Intention To Treat
LENT	Late Effects of Normal Tissue
LINAC	Linear Accelerator
MV	MegaVolts
PTV	Planning Target Volume
RR	Relative Risk
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SLND	Sentinel Lymph Node Dissection
SOMA	Subjective, Objective, Management, Analytic scale
START	Standardisation of Breast Radiotherapy
SweBCG91-RT	Swedish Breast Cancer Group 1991 RadioTherapy-trial

1 Background

1.1 Breast Cancer

1.1.1 Epidemiology

With 1.6 million new cases each year, breast cancer is the most common invasive cancer among women worldwide [1]. In Sweden 7917 new cancers were diagnosed in 2010, which constituted 30% of all female cancer [2]. The breast cancer incidence for women has increased both worldwide and in Sweden. The annual increase in Sweden has been 1.3% during the previous 20 years; however the yearly increase during the previous 10 years is smaller, 0.9%. Known risk factors are: age (two thirds of breast cancer cases occur after the age of 55), heredity (e.g. BRCA 1-2), low age at menarche (before age 11), high age at menopause (after age 54), null parity, high age at first childbirth, BMI > 35 (postmenopausal), using hormonal replacement therapy (HRT) for many years, and exposure to ionizing radiation, especially at a young age [3-5]. Approximately 1500 women die every year in Sweden due to breast cancer. The number of deaths due to breast cancer has been more or less constant for decades, which implies, among other things, that the treatment has become more effective. Furthermore, screening with mammography also contributes to the improvement by finding early breast cancers. The relative five- and ten-year survivals in Sweden are today 89% and 79% respectively compared to 72% and 58% during the 1970s [6]. The prevalence of women who have been treated for breast cancer is therefore increasing; in 2007 the total prevalence was more than 84 000 women in Sweden.

1.1.2 Screening

Mammography has been used since the 1980s in Sweden and the National Board of Health and Welfare (Socialstyrelsen) recommends that women between 40 and 74 years old participate. Mammography increases the chance to find early cancer and thereby increases the chance for cure. The greatest effect is among women between 50 and 69 years old [7].

1.1.3 Treatment

Treatment of breast cancer is often a combination of local treatment (surgery and radiotherapy) to control local disease and systemic treatment against micrometastatic disease (endocrine therapy, chemotherapy, targeted drugs).

Surgery

The American surgeon W.S. Halsted showed in 1894 that women with breast cancer who had a radical mastectomy with removal of the underlying pectoralis muscles and axillary lymph nodes *en bloc* lived longer than women without treatment [8]. During this time period breast cancer was believed to be a locally spreading disease and the surgery performed was extensive. This radical surgery reduced breast cancer mortality, however, giving this extensive and maximum tolerated treatment resulted in extensive morbidity. In the middle of the 20th century a less extensive form of mastectomy, leaving the pectoralis muscles intact, was introduced and the technique of modified radical mastectomy was born [9]. Modified radical mastectomy was then considered as the standard surgical treatment of breast cancer for decades. Ideas that breast cancer could spread systemically instead of only locally and that the surgery should be less extensive were being debated by G. Crile Jr [10] and B. Fisher [11] among others. In the beginning of the 1970s Umberto Veronesi (Italy) and Bernard Fisher (U.S.) initiated randomized studies comparing mastectomy with axillary dissection to breast-conserving surgery with axillary dissection followed by postoperative radiotherapy. These studies did not show any differences in survival. Due to these results the surgically standard practice for early breast cancer was changed to breast-conserving surgery during the 1980s [12-15]. Concerning the removal of the axillary lymph-nodes it was seen that this gives prognostic information and aids in deciding when to carry out adjuvant treatment. It also prevents local tumour recurrences. However, if lymph-node metastases are absent, the benefit of axillary lymph node dissection (ALND) is low or non-existent. Axillary lymph-node dissection can generate more or less arm morbidity depending on the extent of the axillary surgery. During the 1990s the development of less extensive axillary surgery was started and studies using the sentinel lymph-node dissection (SLND) technique were initiated [16-18]. The sentinel node is the first lymph node that drains the tumour site. By injecting a tracer (a radioisotope or blue dye) in the tumour site the first lymph node draining this breast area can be detected and removed [19, 20]. The pathologist examines the lymph-node for metastases preoperatively and if it is free of tumours no axillary dissection is needed. The SLND reduces morbidity compared to ALND with equal risk of axillary recurrences [21, 22].

Today the standard breast cancer surgery is breast-conserving surgery. However, mastectomy is the treatment of choice if the tumour is > 4.0 cm, multifocal tumour, if mastectomy is preferred by the patient, or treatment of a recurrent tumour is indicated. Women with clinically detectable lymph-nodes should have an ALND but otherwise the SLND is the primary surgical procedure for management of the regional lymph-nodes. If the tumour in the breast is multifocal there is some uncertainty if ALND or SLND should be the primary axillary procedure. Giuliano *et al* showed in 2011 that SLND is as good as ALND even when lymph-node metastasis is present in women with early breast cancer [23] and this has also been supported by Galimberti *et al* in Milan [24]. Following these reports there has been a change in the opinion among the physicians towards the view that the axillary dissection often seems to be unnecessary and is almost considered an overtreatment. Umberto Veronesi has summarised the breast cancer treatment movement with the following phrase [25].

" from the maximal treatment tolerable to the minimal treatment effective "

Endocrine Treatment

The first endocrine treatment was done more than a century ago when George Beatson in 1896 described the remission of metastases after bilateral oophorectomy in women with advanced breast cancer. He was of course unaware of the anti-tumour mechanism mediated by the estrogen receptors (ER). The estrogen receptors were first identified by Jensen et al [26] in 1958 and ER are present in 70 to 80% of breast cancer tumours. The ER are intracellular receptors that are produced in most epithelial breasttissue cells and breast cancer cells. These receptors become activated by estrogen, which in turn activates proteins that are important to cell growth and mitosis. Tamoxifen, which was developed in the 1960s, acts as an ER-antagonist in breast tissue and thereby inhibits cell growth. However, Tamoxifen acts as an agonist in some tissues, e.g., in the endometrium which is the explanation of the increased risk of endometrial cancer among Tamoxifen-treated women. Cole et al published the first clinical trial with breast cancer patients in 1971 where they showed a benefit among women with metastatic disease [27]. Ward et al [28] compared doses of Tamoxifen in 1973 and Stoll et al [29] introduced Tamoxifen in the adjuvant setting in 1976. Tamoxifen has relatively mild side effects and has become the most widely used systemic treatment of cancer in the world. The Early Breast Cancer Trialists'

Collaborative Group (EBCTCG) meta-analyses presented in 2011 show that five years of adjuvant Tamoxifen reduces the 15-year risk of breast cancer recurrence and death [30]. This advantage applies only to women with ER-positive disease; women with ER-negative disease show no benefit from using Tamoxifen. Another possible approach to endocrine treatment is to do what Beatson did over 100 years ago, which is to stop estrogen production. The estrogen levels can be reduced by ovarian suppression in pre-menopausal women; either surgically with oophorectomy or medically by using luteinizing-hormone-releasing hormone (LHRH). Among post-menopausal women aromatase inhibitors (AI) stop the production of estrogen by blocking the enzyme aromatase, which turns androgen to estrogen in peripheral tissues of the body.

Chemotherapy

The development of chemotherapy started after World War II and single-agent chemotherapy was first used when treating breast cancer. However, the first reports of benefits when using polychemotherapy came in the 1960s and 70s [31-33]. One of the first established adjuvant chemotherapy combination was cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) [34, 35]. The treatment was further improved with the second generation of polychemotherapy that included anthracyclin. A known combination with anthracyclin is 5-fluorouracil, anthracyclin (epirubicin/doxorubicin), and cyclophosphamide (FAC/FEC) [36, 37]. The third generation of adjuvant chemotherapy was to introduce the use of taxanes and this resulted in an additional increase in the relative survival. In the first decade of the 21st century the first targeted drug, the HER-2 receptor antibody, trastuzumab, (except for endocrine treatment such as e.g. Tamoxifen) was added as a complement to chemotherapy.

Radiotherapy

Ionizing radiation has numerous effects of the cell. An important effect of ionizing radiation is damaging the DNA in the cell nucleus, and it does this whether the cell is a cancer cell or a healthy cell. It works either directly by causing a double-strand break in the DNA thereby causing cell-death or indirectly by ionizing the water in the cell to form hydroxyl radicals that can cause single-strand breaks. The single-strand breaks only cause sub-lethal damage to the DNA so the outcome will depend on the DNA repair capacity

of the cell. Cancer cells often have low DNA repair capacity while the cells in the normal tissue have a higher repair capacity.

The history of radiotherapy starts in 1895 when W.C. Röntgen discovered x-rays and continued with the discovery of radium and polonium by M. Curie in 1898. These discoveries resulted in the building of cancer hospitals around the world, one of which is Radiumhemmet (Stockholm) in 1910, which was equipped with 120 mg radium and an x-ray generator [38], and Jubileumskliniken (Gothenburg) in 1943. The SI unit Gray (Gy), named after the English physicist L.H. Gray, was first used in 1975. In the middle of the 20th century, the use of radium in the field of radiotherapy was replaced by cobalt since cobalt has a much shorter half-life (5.27 y) than radium (1601 y). Cobalt-60 was the common radioactive source in external radiotherapy until the 1980s. The cobalt-machines were replaced during the 1980s and 1990s with linear particle accelerators (LINAC). The Linear accelerator uses high voltage and microwaves to accelerate electrons. In a collision of the electrons and a high Z material, high-energy photons are created. Thus the disadvantages of using an isotope – the steady decrease in activity which requires periodic replacement of the isotope and the condition that an isotope is continuously radioactive and cannot be powered off as can a LINAC - are avoided. In 1971 Godfrey Hounsfield invented the computed tomography (CT), which is fundamental in three-dimensional (3D) dose planning. Prior to the invention of CT, dose planning was based on two-dimensional (2D) x-ray-images. Introduction of the use of CT made it possible to deliver the ionizing radiation in a more precise way to the target, thereby avoiding the surrounding normal tissue. During the 1980s and 1990s great progress was made and most oncology departments changed from using x-ray-images and hand-made 2D dose planning to using CT-images and computer-based 3D-doseplanning.

Between 1949 and 1954, the first randomised study was made of the long-term effects of employing prophylactic x-ray therapy (kilo voltage machines) after radical mastectomy on patients with early breast cancer [39]. The follow-up showed no long-term survival benefit for the group with prophylactic x-ray therapy compared with the group not treated, so the author recommended that x-ray therapy not be used prophylactically. The early studies of radiotherapy showed that there were many undesirable side effects and that the survival benefits from treating the breast cancer with radiotherapy were outweighed by the risks of death from other causes [40]. During the past two decades, several studies have shown that radiotherapy reduces the risk of local recurrences by 60 to 70% but no single study has shown a survival benefit [41, 42]. However, the meta-analyses by the Early

Breast Cancer Trialists' Collaborative Group (EBCTCG) of postoperative radiotherapy following breast-conserving therapy (BCT) or following mastectomy in node-positive patients show a significant benefit in breast cancer-specific survival (+5.4% in absolute terms) and overall survival (+4.4% in absolute terms). The excess mortality (due to effects of radiotherapy) was mainly from heart disease and lung cancer. The breast cancer-specific survival remained unchanged but the overall survival increased to 5.3% when the oldest radiotherapy studies were excluded. However, studies using a shorter follow-up time most often underestimate the number of cardiac events. The EBCTCG concluded that, "about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided at 5 years". For example, a reduction in the 5-year local recurrence risk of 12% would result in a 15-year reduction in breast cancer mortality of 3%, i.e. a 4:1 ratio [41]. In 2007 Bartelink *et al* [43] showed that a fractionated boost dose of 16 Gy to the original tumour bed led to improved local control in all age groups, with the largest benefit in young women, but with no difference in survival. Severe fibrosis was increased in the boost group. Results from randomised studies comparing hypofractionated radiotherapy with >2.0 Gy/fraction to conventionally fractionated radiotherapy with 2.0 Gy/fraction to 50 Gy have recently been published [44]. Whelan *et al* [45] presented 10-years of results comparing results using 2.66 Gy to 42.5 Gy with the results from conventional fractionation and found similar results regarding tumour effect and normal tissue complications. START-A and -B (Standardisation of Breast Radiotherapy) [46, 47] compared results from conventional radiotherapy with those from 3.2 Gy to a total dose of 41.6 Gy, 3 Gy to 39 Gy, and 2.66 Gy to 40 Gy but with a shorter follow-up.

The recommendations by the Swedish Breast Cancer Group (SweBCG guidelines) are to use external radiotherapy to the breast after breast-conserving surgery (BCS) and to the thorax after mastectomy if the tumour diameter > 5 cm or if regional radiotherapy has also been recommended. The standard irradiation schedule is 2 Gy per fraction, 5 days per week to a total of 50 Gy or a hypofractionation schedule (after BCS only) with 2.66 Gy/fraction to a total of 42.5 Gy (> 50 years of age in Göteborg). An additional radiotherapy boost, of 16 Gy in 2 Gy-fractions, to the primary tumour site is recommended in young women ($\leq$ 40 years of age) or if the tumour has not been removed radically. Regional radiotherapy to the axillary and the supraclavicular lymph nodes is recommended if $\geq$ 4 lymph node metastasis are found or if $\geq$1 lymph node metastasis are found among women of $\leq$ 40 years age, if the tumour is a grade III, has vascular invasion, or if the

ratio of number of lymph node metastasis divided by the number of examined lymph nodes is > 20%.

1.2 Radiotherapy-related side effects in normal tissue

The aim of radiotherapy is to kill the tumour cells without causing unnecessary damage to the normal tissue. Increasing the radiation dose increases the probability of killing the tumour cells (TCP, tumour control probability); however this will increase the probability of damaging the surrounding healthy tissue as well (NTCP, normal tissue complication probability). The ratio between TCP and NTCP is the therapeutic ratio [48] and we always strive for a large ratio. The following section contains information regarding the side effects of radiation therapy.

The side effects after radiotherapy are normally divided into two parts, the first part comprises the early side-effects that appear during or within weeks after radiotherapy, the second the late side-effects that appear months or years after treatment [49]. The side effects mainly develop locally in the irradiated tissue or organ, i.e. irradiation generally does not produce a systemic side effect as drug therapies do. The early side effects start to develop directly after treatment and are most readily apparent in tissues with rapidly proliferating cells, e.g. the skin, the haematopoietic system, or the gastrointestinal canal. The symptoms become apparent when mature cells that are lost due to normal tissue turnover are not replaced since the stem-cells or precursor cells have been damaged [50]. Chemotherapy has a similar effect on the rapidly proliferating cells and this is why concomitant use of these two treatment modalities often leads to increased early normal tissue toxicity [51]. The early side effects are usually reversible as opposed to the late effects that tend to be irreversible. Ionizing radiation do not only cause cell killing but it also activate a cascade of cytokines as the transforming growth factor-β (TGF-β). Furthermore, radiation damages endothelial cells also activtes pro-fibrotic cytokines (as TGF-β). TGF-β seems to be important when explaining the radiation fibrosis that is a part of the late side-effects. Activation of TGF-β leads to increased extracellular matrix and collagen deposition. This radiation induced fibrogenic process is perpetuated over a long period of time [49].

A universal link between early and late side effects has not yet been established [51, 52]. For some tissues such as the intestinal system and the mucosa there seems to be a relation but for others, e.g. the skin, it is less clear [53-55]. The response of normal tissue to radiotherapy cannot (so far) be predicted by *in vitro* tests [52, 56-58]. The explanation for this is probably that the *in vivo* situation is too complex with e.g. cytokine response and collagen deposition (i.e. concerted biological response) and cannot be mimicked in the laboratory [49, 59, 60].

Organ-specific late side-effects

A feared side late effect after breast cancer radiotherapy is the cardiotoxicity that has been known for decades [61]. The pathophysiology of radiation-induced myocardial damage is mainly due to endothelial cell damage in microvessels, leading to perfusion defects and inflammatory infiltrates. However, radiation also damages the major arteries, leading to an accelerated development of atherosclerosis [62]. The risk has been most apparent when treating left sided breast cancers and if the internal mammary chain is included in the field [63-66]. With modern dose planning the cardiotoxic side effects seem to be decreased, but since the follow-up time to date has been shorter a lower incidence of cardiotoxicity is to be expected [41, 67-69]. In 2011, McGale et al presented the incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden [70]. They found that breast cancer radiotherapy has, at least until recently, increased the risk of developing ischemic heart disease, pericarditis and valvular disease. However, in the latest report from EBCTCG in 2011 the extra mortality due to cardiotoxicity seems to be very small (EBCTCG 2011). Dose-volume response analyses have been made, but so far no clear guidelines exits [71].

Often described late effects in breast radiotherapy trials comparing boost and hypofractionation are skin telangiectasia and fibrosis of subcutaneous tissue, which could lead to loss of volume and retraction of the breast [44-46, 53, 72-74]. We know that increased doses to the breast, given as a boost, increase the risk of breast fibrosis [72, 75]. Pain in the breast area has been described as a late toxicity effect associated with radiotherapy, but the mechanisms behind this are not known [76-80].

The risk of radiotherapy-induced brachial plexus neuropathy (BPN) has been reported since the late 1960s [81]. Brachial plexus neuropathy can result in paraesthesia, pain, and weakness of the arm. The pathophysiology of brachial plexus neuropathy is due to fibrosis of connective tissue around peripheral

nerves, damage to capillary blood vessels of the media of small arteries resulting in ischemia as well as extensive thickening of epi- and perineurium [82].

Lung fibrosis is mostly associated with large lung volumes and concomitant chemotherapy. Clinical symptoms of lung fibrosis [46, 74, 83-85] are nonspecific and include e.g. cough, dyspnoea and fatigue. The underlying pathophysiology is similar to fibrosis that occurs in other tissues, with profibrotic cytokines, such as TGF-b IL-1 and IL-6, playing a role.

Having had an axillary dissection instead of a sentinel node biopsy increases the risk for oedema in the arm, and the risk increases further when radiotherapy to the regional lymph nodes is added [83, 86, 87].

Rib fractures do not seem to be a significant problem after breast cancer radiotherapy, this side effect is more important after e.g. hypofractionated stereotactic radiation of lung cancer [46, 83, 85, 88-90].

Two important concluding summaries have been published, one by Emami [91] and the other by QUANTEC **(**Quantitative Analyses of Normal Tissue Effects in the Clinic) [92] in order to create clinical guidelines concerning tolerance doses of organs-at-risk.

Of importance, although not within the scope of this thesis, are the secondary cancers due to breast cancer radiotherapy treatment; e.g. sarcoma [93], lung cancer [94], and contra lateral breast cancer [95]. The pathogenesis of secondary cancer is however linked to the mutagenic response of the ionizing radiation (e.g. if the DNA-damage is repaired incorrectly) rather than being derived from, e.g., the fibrogenic response.

2 Aim

The overall aim of the research on which this thesis is based was to identify and quantify self-reported long-term symptoms/side-effects caused by breast cancer irradiation and to correlate these effects to patient and treatment-related risk factors. Furthermore, we wanted to investigate how the dose-volume distribution of ionizing radiation delivered to a certain anatomical volume contributed to the occurrence of a certain symptom, i.e. a dose-volume response analysis.

2.1 Specific Aims

Paper I

To compare the occurrence of eight pre-specified symptoms/side-effects groups (below) among women who were randomised to receive tangential breast irradiation or not after breast conserving surgery with axillary dissection due to breast cancer 10 to 17 years earlier.

With decreasing likelihood, we hypothesised that radiation would induce:

1 - pain in the breast,

2 - oedema in the breast or the upper limb,

3 - disturbances of skin sensation on the breast,

4 - erysipelas in the upper part of the body,

5 - symptoms from the heart,

6 - symptoms from the lungs,

7 - fractures in the ribs, and

8 - decreased shoulder or arm mobility.

Paper II

Based on the results in paper I and from the literature we know that radiotherapy increases the risk of long-term breast pain. In this paper we investigate risk factors that could increase the risk of reporting breast pain among women who received irradiation after breast conserving surgery 3 to 17 years earlier.

Paper III

In this paper we wanted to investigate if modern standard radiotherapy, i.e. 3D dose planning and 2.0 Gy fractionation to the regional lymph-nodes, resulting in radiotherapy fields covering the nervous plexus brachialis, increases the risk of reporting neuropathy 3 to 8 years later.

Paper IV

Based on the results in paper III and from the literature we know that regional radiotherapy increases the risk of paraesthesia. In this paper we investigated dose-volume predictors after irradiation of the plexus brachialis for the development of paraesthesia among breast cancer patients.

3 Patients and Methods

3.1 Patients

Cohort 1

From 1991 through 1997, 1187 women participated in the multi-institutional SweBCG91-RT (Swedish Breast Cancer Group 1991-RadioTherapy trial). Women with stage I-II lymph node-negative breast cancer (T1-2N0M0) who had been treated with breast conservation and axillary dissection were randomly assigned either to a group receiving no further treatment or to a group receiving postoperative radiotherapy. We included women from the SweBCG91-RT trial who lived in the West and South health-care regions. The third and last health-care region, Uppsala-Örebro, only included 43 women. These were excluded for cost-efficacy reasons. To increase the quality of the data and to ensure a high participation rate, we included women born in 1931 or later. We excluded women who had died, had a breast cancer recurrence, had a cancer treatment during 2007, did not speak Swedish, or were not living in Sweden. After exclusion we identified 422 women (Figure 1).

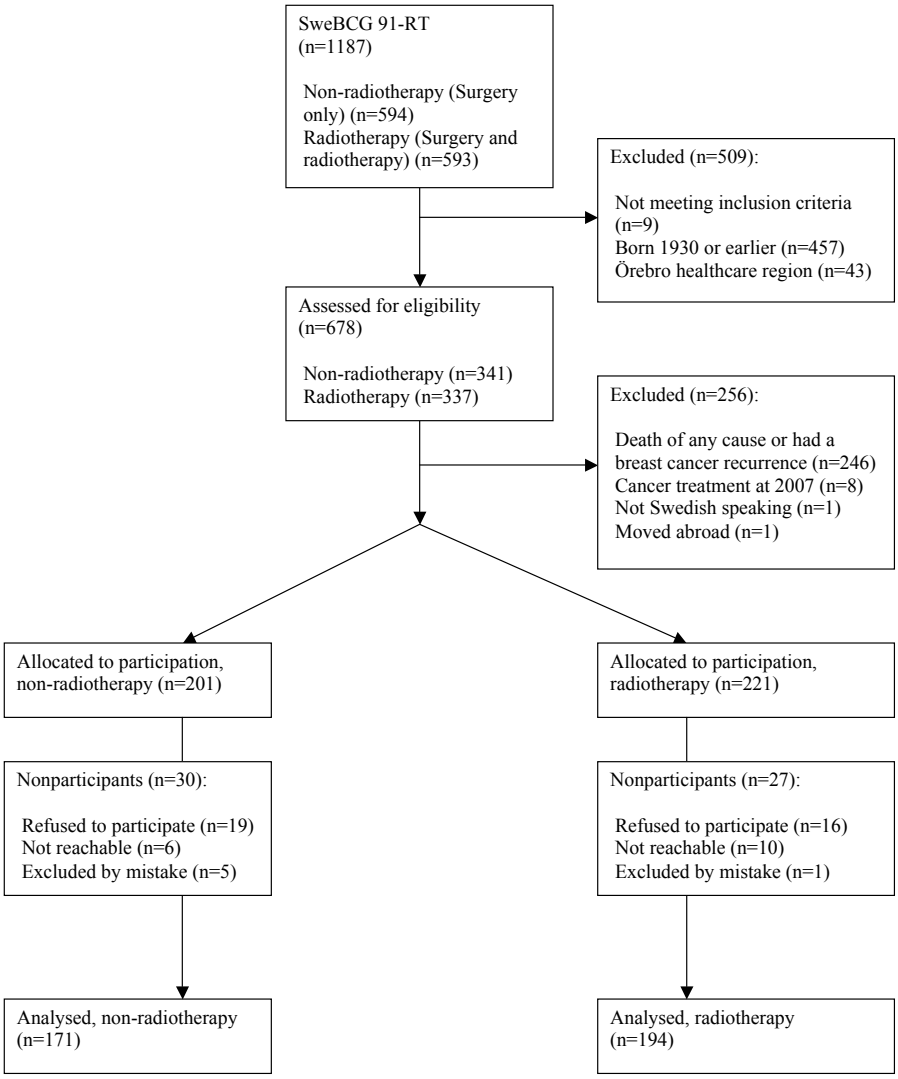


Figure 1: A flowchart of cohort one, i.e. the patients included in the SweBCG91-RT trial, presented according the intention-to-treat (ITT). Women with breast cancer who had a breast conserving surgery and axillary dissection were randomised to receive or not to receive postoperative radiotherapy.

Cohort 2

Through medical records we identified the women who had breast cancer radiotherapy based on a 3D-dose plan between mid-1999 and 2004 at Sahlgrenska University Hospital, Gothenburg. At the Sahlgrenska University Hospital, we started to use 3D-dose planning for all our breast cancer treatments from mid-1999 and onwards. During the time period 1999 to 2004, 2565 women were consecutively registered as treated with radiotherapy due to a primary breast cancer in Gothenburg. Among these treatments, we were unable to reactivate 130 archived dose plans due to technical reasons. To ensure a high participation rate we excluded women born in 1930 or earlier (n=263). We also excluded women who had died, had a breast cancer recurrence, had another radiotherapy treatment registered, had a cancer treatment during the last year (i.e. 2007/08), had not completed the planned radiotherapy treatment, suffered from dementia, did not speak Swedish or who were not living in Sweden (n=396). Of the 2565 women we identified 1776 eligible women. Of these 1776 women, 1372 women had the most common treatment with breast-conserving surgery followed by postoperative tangential breast irradiation without any boost or regional radiotherapy. Due to cost-efficacy considerations we randomly excluded half (685 excluded out of 1372) of the women with the most common treatment. Thus there were 1091 women remaining for the study (Figure 2).

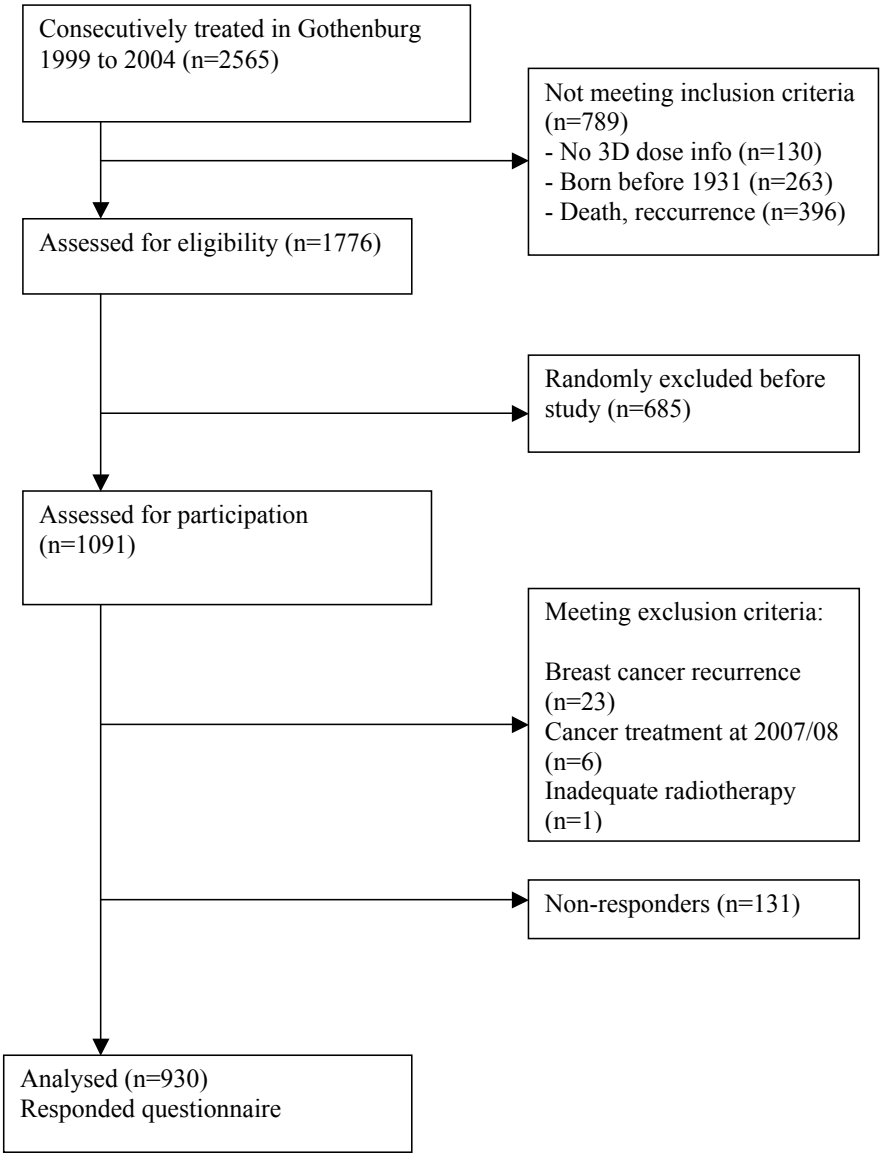


Figure 2: A flowchart of cohort two, i.e. the patients who had breast cancer radiotherapy treatment between 1999 and 2004 at Sahlgrenska University Hospital, Gothenburg.

Patients in paper I

In paper I we analysed the data from the women in cohort one according the intention to treat (ITT). Non-radiotherapy (n=171) and radiotherapy (n=194), in total n=365 women.

Patients in paper II

In paper II we analysed the data from the women with breast-conserving surgery with radiotherapy in cohort one and two. The women that had radiotherapy from cohort one were included according received treatment and not according ITT. Five women in cohort one had not received treatment according to ITT, and of these five, three did not receive their radiotherapy as intended and two received radiotherapy that they should not have received (n=194–3+2=193). The women from cohort two (n=930) that had a breast conserving surgery were included (n=684) and the women that had had a total mastectomy were excluded (n=246). In total 193 + 684 = 877 women.

Patients in paper III

In paper III we analysed the data from the women in cohort two. Of these 930 women, 111 had had the older 2.4 Gy fractionation schedule and were excluded. Five more women were excluded because we lacked information about whether axillary dissection had been performed. Of the remaining 814 women, 192 women had had axillary dissection and regional radiotherapy, 509 women had had axillary dissection without regional radiotherapy, and 113 women had had neither axillary dissection nor regional radiotherapy.

Patients in paper IV

In paper IV we analysed the data from the women in cohort two that had axillary dissection with regional radiotherapy in 2.0 Gy fractions (n=192) and used women that had axillary dissection without regional radiotherapy as a reference group (n=509).

3.2 Treatments

3.2.1 Surgery and Radiotherapy

The women underwent breast-conserving surgery or mastectomy with an axillary lymph node dissection of level I and II or a sentinel lymph node biopsy. Radiotherapy was given either 4 days a week over 5 weeks, 2.4 Gy per fraction, to a total target dose of 48 Gy or 5 days a week over 5 weeks, 2.0 Gy per fraction, to a total target dose of 50 Gy. In addition, women with four or more axillary lymph node metastases also received regional radiotherapy i.e. radiotherapy to the supra/infraclavicular lymph nodes and the level III axillary lymph nodes. The lymph nodes were treated with 46 to 50 Gy, given in 2.0 Gy fractions per day. Young premenopausal women received an additional boost to the primary tumour site of up to 16 Gy, given in 2.0 fractions per day. The patient had a supine treatment position.

Cohort one: The target was defined as the remaining breast parenchyma, without the regional lymph nodes. The treatment fields had a margin of 1–2 cm with respect to the breast parenchyma and were also limited to the ipsilateral breast, not crossing the medial line. This treatment technique limited the volumes of lung and heart receiving full dose. No bolus was used. The dose-specification point was defined at the centre of the target volume. The minimum and maximum doses in the target volume were defined according to the International Commission on Radiation Units and Measurements [96] and should have been within 93–110% of the specified dose. All patients had individual computerised dose planning with wedge compensators used to achieve a uniform dose. At one of the departments a two-dimensional planning technique, based on three CT slices, was used throughout the whole study period. At the other three departments the same two-dimensional technique was used in the first year, but by 1993 all women had three-dimensional dose planning (TMS, Helax AB) based on multiple CT slices with intervals of typically one centimetre.

Cohort two: All patients had three-dimensional dose planning (Varian Medical Systems Inc., Eclipse/Cadplan) based on CT scanning with slice thickness of 5 to 10 mm. For women without regional treatment the PTV (Planning Target Volume) included the remaining breast/thoracic wall (Figure 3,4). Tangential photon beams or an electron beam was used having the isocenter located centrally in the breast/thoracic wall. For women with regional treatment the PTV included the breast/thoracic wall and supraclavicular fossa/the top of the axilla (level III) (Figure 5). A common isocentre for all fields was located in the junction between the supraclavicular

fossa/the top of the axilla fields and breast/thoracic wall fields. A high-energy linac with dual photon beams and electron beams was used. All treatment plans were individually optimized. The supraclavicular fossa/the top of the axilla volume was planned with opposed fields; AP (anterior-posterior) field of 6 MV (megavolts) with a relative beam weight of about 1.0, PA (posterior-anterior) field of 15 MV with a relative beam weight of about 0.4. The dose was prescribed in the centre of the supraclavicular fossa/the top of the axilla part of the PTV and normalized to this point. The maximum dose was 105 to 108 % (specified as percentage of prescribed dose) and located about 1 cm below the skin (not in isocentre plane). The breast was planned with tangential 6 MV photon beams tilted 5 to 10 degrees in order to minimize divergence of the fields. The dose was prescribed in the centre of the breast and normalized to this point. The thoracic wall had either tangential fields or a combination of electron and photon beams. The electron beam had the same isocentre as the other fields. In the isocentre plane between the electron beam and the supraclavicular fossa/the top of the axilla fields the maximum dose at 1 to 2 cm below skin was usually 110 % (accepted range up to 115 %). A bolus of typically 5 mm to increase the superficial dose was always used after mastectomy but was generally not used after breast-conservation except in 13 patients with superficial tumours.

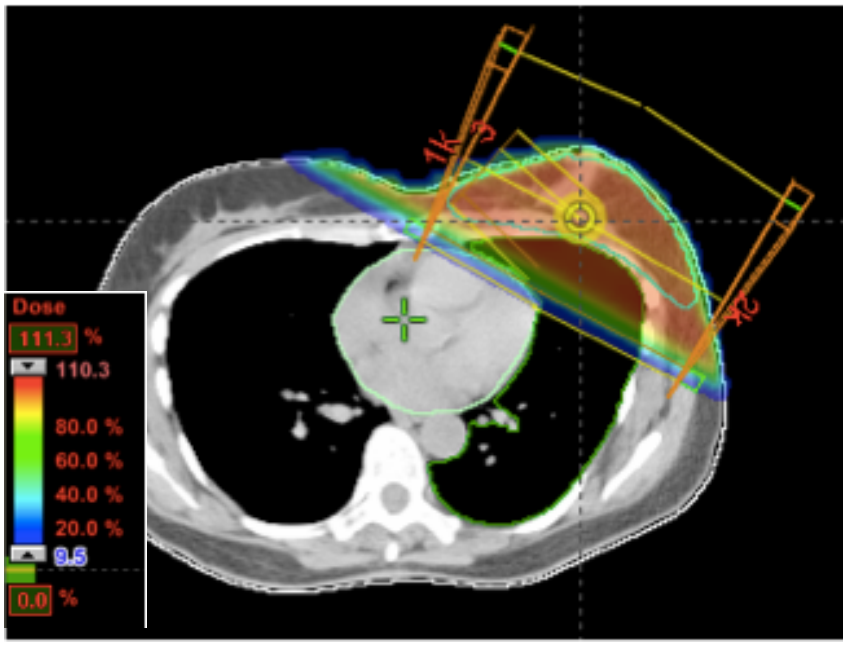


Figure 3: A left side breast cancer treatment plan, shown in a transverse plane.

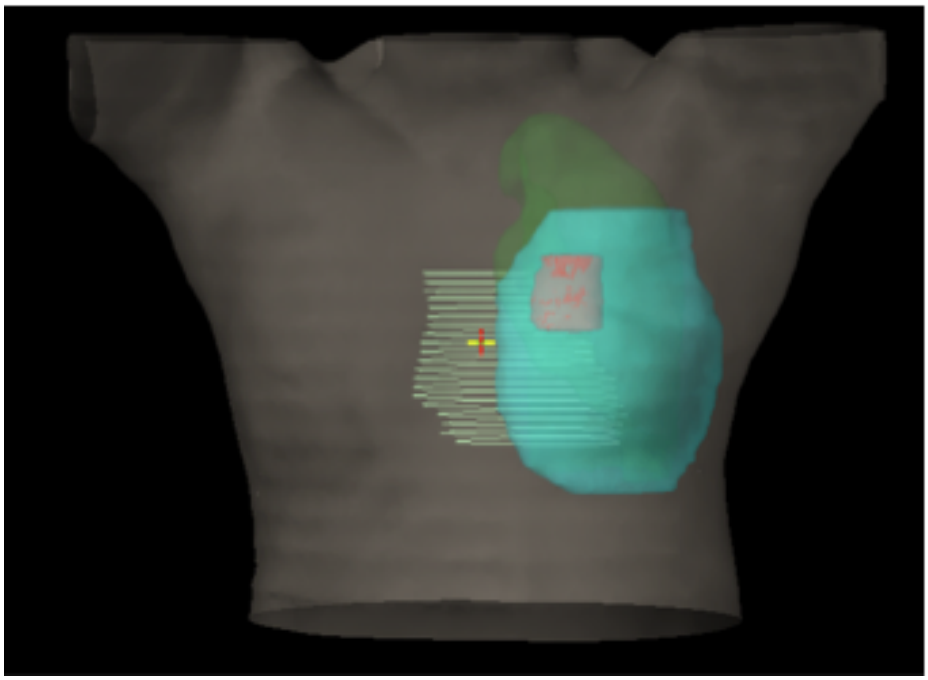


Figure 4: The figure shows a reconstructed coronal view. Left side breast PTV (blue) and CTV (red). Organs at risk: Lung (green) and heart (yellow lines).

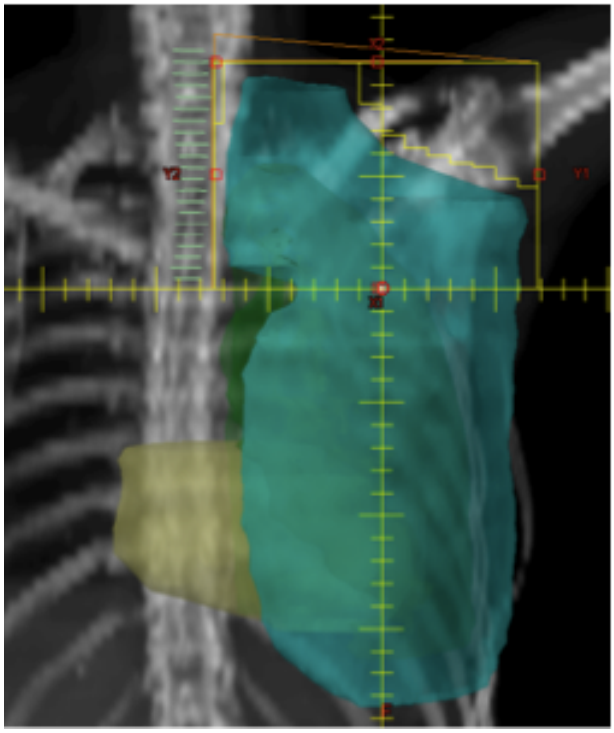


Figure 5: The figure shows a reconstructed coronal view. Left side thorax PTV (blue) includning regional lymph nodes. Organs at risk: Lung (green) and heart (yellow).

3.2.2 Systemic treatments

The recommendations in the SweBCG91-RT trial were that women with an estrogen receptor-positive tumour with a diameter of more than 2 cm should receive endocrine treatment (Tamoxifen) and that premenopausal women with an estrogen receptor-negative tumour of more than 2 cm should receive chemotherapy (cyclophosphamide, methotrexate, fluorouracil). In practice very few of the women in the SweBCG91-RT trial had any systemic treatment since they had an early breast cancer without lymph node metastases.

The women in cohort two were treated according to regional healthcare guidelines. Chemotherapy (cyclophosphamide, methotrexate, and fluorouracil or fluorouracil, epirubicin, and cyclophosphamide) indications for premenopausal and postmenopausal women were either one of:

1 – Lymph-node metastases or 2 – Two of the following if N0; a primary tumour diameter of more than 2 cm or endocrine receptor-negative tumour or S-phase ≥12%.

Generally, women with a receptor-positive tumour received endocrine treatment (Tamoxifen). Older postmenopausal women received an individual treatment plans based on their physical status.

3.3 Methods

3.3.1 Development of questionnaire

We were interested in learning whether or not the breast cancer-irradiation caused women problems many years after treatment. Our intention was to achieve the self-assessed, not physician-assessed, descriptions of symptoms and if these symptoms affected daily life. We wanted to develop the questionnaire from the beginning, based on semi-structured interviews, since we wanted to create a wider picture and to cover aspects in addition to those in current questionnaires [97-100]. We intended to collect all information regarding the symptoms/side effects that the women experienced in their daily life years after treatment. The ambition was to create a questionnaire in which one question represents one phenomenon, instead of the more common

questionnaire where the items are summarized to global scores and represented with a number. The development of the questionnaire was done according to the established procedures at the Division of Clinical Cancer Epidemiology [101-104].

Interviews

The qualitative phase lasted approximately 1.5 years and was the foundation of the study. We interviewed women that had undergone breast cancer surgery and postoperative radiotherapy three to 20 years earlier, 1985 to 2003. The women were first contacted by mail and asked if they were willing to participate in an interview. A few days after the first contact, each woman was contacted again by phone and asked if she would be willing to participate. Those who volunteered were interviewed primarily in their home or otherwise at the research unit. The interviews were recorded and performed in a semi-structured way by focusing on the informant's present situation, current symptoms, effects on daily life, social functioning and coping strategies. The goal was to continue interviewing until no new information was identified (saturation) and in total 22 women shared their experiences. A secretary continuously prepared word-by-word transcripts from the interview recordings.

Questionnaire

Based on interviews, our clinical knowledge, and the literature a questionnaire was constructed. The different themes, sorted into specific areas, were formulated into questions and divided into sections. We developed questions asking about symptoms on both the left and the right side of the body, i.e. both the treated side and the opposite part of the body. In the analysis phase we used the answers from the treated side. We also included questions asking if these symptoms affected daily life. When formulating the questions we aimed at using the words/phrases that the women used during the interviews. Information on variables reflecting potential confounding and effect-modifying factors such as concurrent diseases and treatments were also collected. The questionnaire was extensive and consisted of 240 questions that were arranged in the following sequence

1. Breast cancer treatment. Surgery, radiotherapy, chemotherapy, endocrine treatment and disease recurrences: questions 1.1-1.11
2. Psychological issues and wellbeing: questions 2.1-2.12

3. Mobility and strength: questions 3.1-3.27
4. Oedema: questions 4.1-4.66
5. Pain: questions 5.1-5.101
6. Paresthesia: questions 6.1-6.5
7. Breast reconstruction: questions 7.1-7.5
8. The throat: questions 8.1-8.12
9. Heart and lungs: questions 9.1-9.25
10. The skin: questions 10.1-10.23
11. Sexuality: questions 11.1-11.5
12. Education, martial status, co-morbidity: questions 12.1-12.33
13. Evaluating the perception of participation: questions 13.1-13.8

We inquired about the frequency and intensity of a symptom when appropriate. For example: Have you felt pain in your left breast in the previous six months? The answer category was: “No”, “Yes, on occasion”, “Yes, at least every month”, “Yes, at least every week”, “Yes, at least three times every week”, “Yes, every day”. In addition, there was space for supplementary comments within each section. For evaluating the perception of participation seven questions were included. For example: Do you believe it is valuable to conduct a study like this? “No, not at all”, “Yes, somewhat”, “Yes, moderate”, “Yes, much”.

Face-to-face validation

At this stage, to ensure that all questions and response alternatives were fully understood, an investigator accompanied women treated for breast cancer while they filled out the questionnaire, i.e. face-to-face validation. This led to the formulation of new versions and the process continued until the participants suggested that the questions covered all their experienced symptoms and was easily understood. The questionnaire was tested for face-to-face validation on totally 20 women.

Pilot study

In a pilot study comprising 32 women treated for breast cancer we estimated a likely participation rate and whether or not the women would leave certain questions unanswered. After receiving 30 of 32 questionnaires we proceeded to the main study. The Regional Ethic Committee in Gothenburg approved of the study.

Data collection

From October 2007 to April 2008, an introductory letter was sent to the women explaining the objects of the study emphasizing that participation in the study was voluntary. Three days later an interviewer phoned each informant. Those giving informed oral consent to participate received a postal questionnaire along with a letter and additional information. Ten days later, a thank-you card was sent to show appreciation or to serve as a reminder. Fourteen days later an interviewer called those who had not returned the questionnaire, giving the women the opportunity to ask questions or decline further participation. To ensure anonymity the questionnaires were coded, making it possible to match responses to the treatment given.

Data entry

Transfer of all data from the questionnaire answered by cancer survivors was performed using the freeware data and validation program EpiData 3.1 (www.epidata.dk).

Treatment plan reactivation

At Sahlgrenska University Hospital, Gothenburg, we started to use 3D-treatment planning for all breast cancer treatments from the 1999 onward. In our study we reactivated the treatment plans and made copies that we used to investigate how the dose-volume distribution of ionizing radiation delivered to a certain anatomical volume had contributed to the occurrence of a certain symptom, i.e. a dose-volume response analysis.

3.3.2 Delineation of the brachial nerve

The patient had a supine treatment position. An individual vacuum form connected to an arm holder was made with the intent of having the sternum as nearly horizontal as possible. The patient had to hold the arm on the treatment side on the holder beside the head. The contralateral arm was placed along the body. Together with a radiologist we modified the guidelines regarding contouring of the brachial plexus by Hall *et al* and applied them to breast cancer patients with an elevated ipsilateral arm. To contour the brachial plexus we used a 5-mm diameter paint tool. The contouring started at the neural foramina from C5 to T1 and the delineation

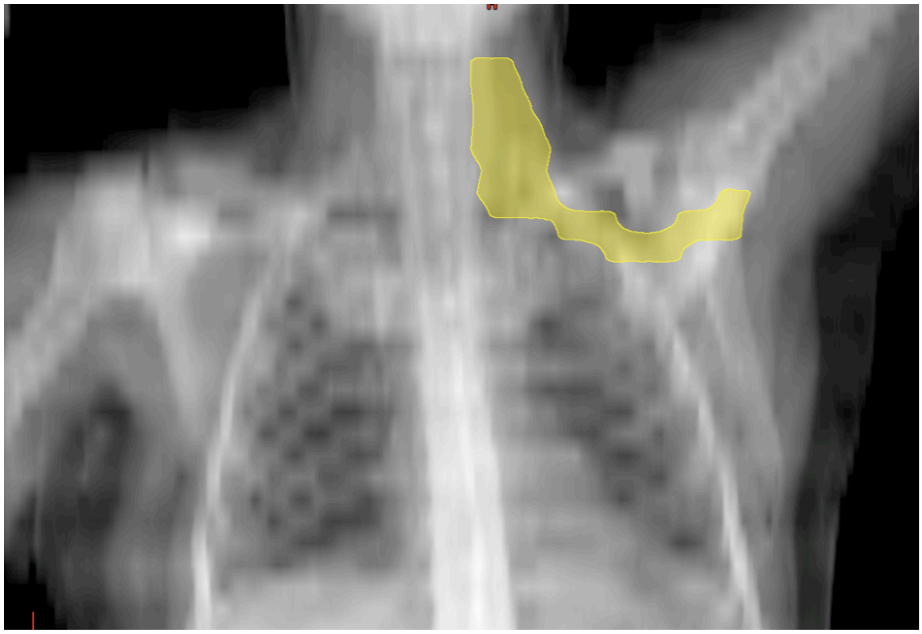


Figure 6: Reconstructed coronal view of the delineated brachial plexus.

extended from the lateral border of the spinal canal to the space between the anterior and middle scalene muscles. If the neural foramen was lacking on the CT slice the space between the anterior and middle scalene muscles was delineated. Further contouring went between the first rib and the clavicle, behind the minor pectoral muscle (following the subclavian artery when possible), below the coracoid process and in front of the subscapularis muscle (Figure 6,7).

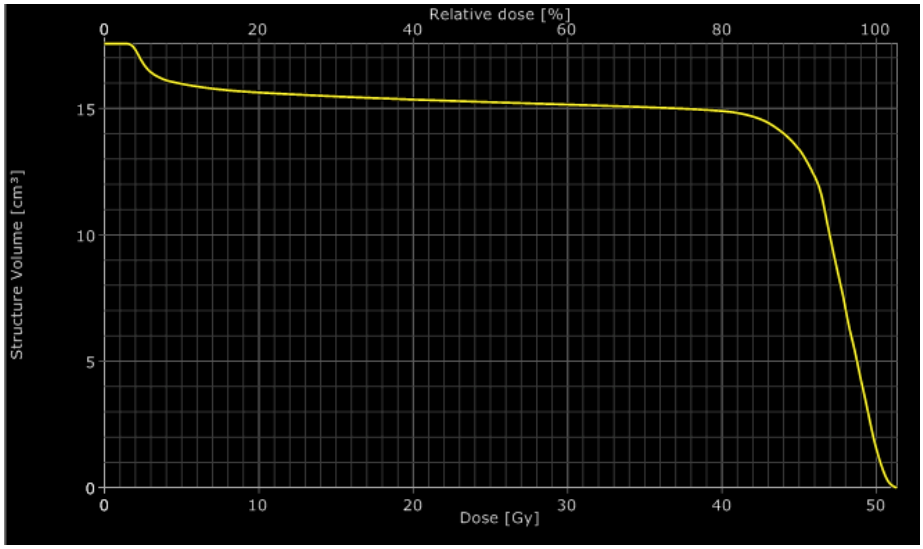


Figure 7: Dose Volume Histogram (DVH) of a delineated brachial plexus.

3.3.3 Statistical analyses

To gain a pedagogic clarity the outcome variable was often dichotomized. The results are presented as relative risks (RR). We adjusted these relative risks, when suitable, using the SAS procedure GENMOD (SAS version 9.2; SAS Institute Inc., Cary, NC) with binomial distribution and logarithmic link function. The relative risks were considered as 'statistically significant' when the 95% confidence interval (CI) did not contain 1.00, i.e. the reference value. See manuscript I-IV for details of statistically analyses of each study.

4 Results

Paper I:

Of the 422 eligible women 365 (86%) returned the questionnaires. Participation rates were similar for both groups (BCS+RT 194/221 [88%] vs. BCS 171/201 [85%]). Five women who completed the questionnaire had not received treatment according to randomisation (the intention-to-treat). Three women did not receive their radiotherapy as intended and two received radiotherapy that they should not have received. In the analyses, the results were identical or similar whether these women were included or not. The results are presented according to the intention-to-treat. Mean age when completing the questionnaire was 67 years and the mean time since treatment was 14 years. The tumour characteristics were closely similar in the two groups as well as in comparison to the original study group with 1187 women.

For six symptom groups (oedema in breast or arm, erysipelas, heart symptoms, lung symptoms, rib fractures, and decreased shoulder mobility) we found a similar occurrence in both groups.

However, the first hypothesis that radiation would induce breast pain was confirmed. In the group with postoperative radiotherapy 35.8 percent reported occasional pain in the treated breast compared to 19.9 percent in the non-radiotherapy group with an absolute difference of 15.9 percent, RR 1.80 (95% CI 1.26-2.57). Corresponding figures for occurrence at least once a

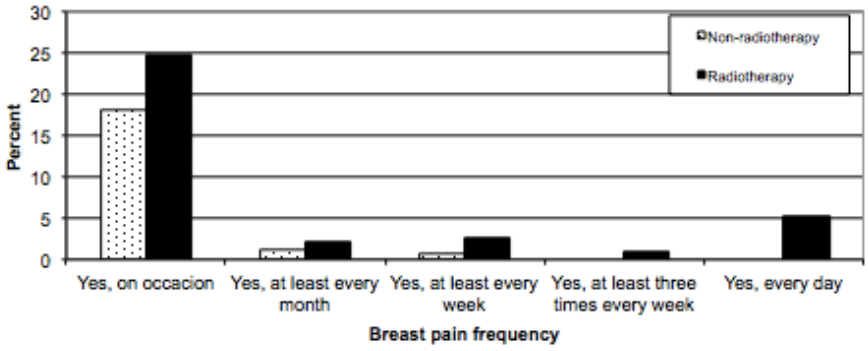


Figure 8: Occurrence presented by each response category. The figure shows the absolute percent based on all women in each group, but shows only the women who answered yes.

week were 8.8 percent versus 0.6 percent with an absolute difference of 8.2 percent, RR 15.1 (95% CI 2.03-112). Touching and pressure on the treated breast were reported to induce breast pain more often in the irradiated group. Examining other cut-off points did not alter the results in a way that would lead to an alternative interpretation of effects (Figure 8). Analyses restricted to women who did not have chemotherapy showed similar results.

The third hypothesis regarding disturbances of skin sensation was also confirmed. The irradiated group reported a higher occurrence of hypersensitivity in the skin on the treated breast, 5.2% versus 0.6% in the surgery only group, RR 8.81. The adjusted relative risk resulted in estimates ranging from 7.92 to 8.83. Sensitivity to sun exposure on the treated side, compared to the contra lateral breast, was more common in the irradiated group, 7.3% versus 1.2%, RR 6.33. In the group with postoperative radiotherapy 21.9% reported occasional pain in the skin compared to 11.8% in the non-radiotherapy group with an absolute difference of 10.1 percent, RR 1.86 (95% CI 1.14-3.04).

We found no statistically significant differences between the groups for whether symptoms affected daily life or the use of analgesics.

- I have not been able to wear a bra for many years due to discomfort.
Radiotherapy, 16 years ago.
- It is not easy to find a comfortable bra since my breast always aches or hurts. *Radiotherapy, 11 years ago.*
- If I am hit in my breast, even if not very hard by an elbow, for example, it hurts a lot. *Surgery only, 10 years ago.*
- My breast has been aching since 1996. *Radiotherapy, 11 years ago.*
- When I wear thin clothing in the sun it burns like fire in the skin on my breast. *Radiotherapy, 13 years ago.*
- The skin on my breast burns or stings when I am in the sun wearing thin clothing. *Radiotherapy, 15 years ago.*
- During the years since being treated, I have learned to adapt and to cope with the pain and discomfort that the surgery and radiotherapy caused me.
Radiotherapy, 14 years ago.

- ...but this is not so important since I have been cured of cancer.
Various women.

Figure 9: A sample of comments in the questionnaires written by the women in cohort one.

Paper II

We received 193/221 (87%) questionnaires from the women in cohort one and 684/806 (85%) questionnaires from the women in cohort two. In total 877/1027 (85%) of the women had returned their questionnaire. Of these, 873 women answered the question in the questionnaire regarding breast pain. The mean age at treatment was 55 years, range 28 to 73 years. The occurrence of breast pain at least every week among the 873 women in this study who had breast-conserving surgery and radiotherapy was 13.2%, three to 17 years after treatment.

Among women with breast pain 30% consumed analgesics every week compared to 9% among women without weekly breast pain (RR 3.5; 95% CI 2.5-5.1). Furthermore in the group with breast pain, discomfort and pain resulted in: affected wellbeing (RR 4.6; 95% CI 3.3-6.4), sleeping trouble (RR 4.7; 95% CI 3.3-6.5), avoidance of wearing a bra (RR 4.0; 95% CI 2.7-5.7), discomfort due to tight clothing (RR 3.2; 95% CI 2.6-4.0), difficulties buying fitting clothing (RR 3.5; 95% CI 1.7-7.3), and affected daily activity (RR 4.1; 95% CI 2.9-5.9).

There was a statistically significant relation between younger age and a higher occurrence of breast pain (Figure 10). Among women up to 39 years of age at treatment, 23.1% experienced pain in the breast at least every week, compared to 8.7% among women older than 60 years, giving an absolute difference of 14.4% (RR 2.66; 95% CI 1.33-5.36). The annual relative risk reduction was 0.96 (95% CI 0.94-0.98). When we examined the time since treatment we found that there was a statistically significant relation to breast pain. Women for whom a longer period of time had passed since treatment reported breast pain significantly less often than did the other women. The occurrence of breast pain was reported with the lowest frequency, 8.8%, among women treated more than a decade earlier and the highest, 15.5%, among women treated three to five years earlier (RR 1.75; 95% CI 1.05-2.93). The annual relative risk reduction was 0.93 (95% CI 0.88-0.98). Chemotherapy increased the risk of having breast pain from 11.7% to 20.1% (RR 1.72; 95% CI 1.19-2.47). However, in the multivariable model only age at treatment and time since treatment were statistically significantly related to the occurrence of breast pain. In the multivariable model chemotherapy did not increase the risk of reporting breast pain.

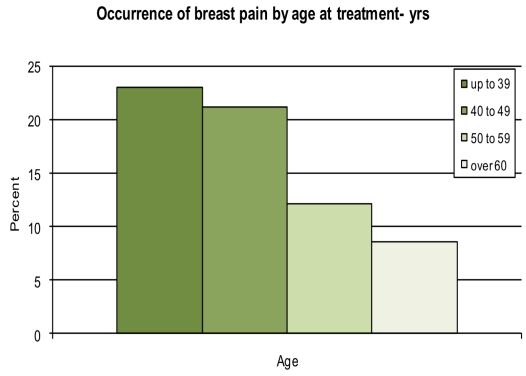


Figure 10: Breast pain occurrence by age group.

No statistically significant associations were found between the two different radiotherapy fractionation schedules with 2.4 Gy to 48 Gy or with 2.0 Gy to 50 Gy and the occurrence of breast pain (RR 0.85; 95% CI 0.54-1.36). There was no significant relation to breast pain regarding the other potential effect modifiers; endocrine treatment, tumour size, photon energy, radiotherapy boost, regional radiotherapy to the lymph nodes, axillary dissection, overweight, smoking, marital status, parity, and level of education.

Paper III

We received 930/1091 (85%) questionnaires. Of these 930 women, 111 had had the older 2.4 Gy fractionation schedule and were excluded. Five more women were excluded because we lacked information about whether axillary dissection had been performed. Of the remaining 814 women, 192 women (24%) had had axillary dissection and regional radiotherapy, 509 women (62%) had had axillary dissection without regional radiotherapy, and 113 women (14%) had had neither axillary dissection nor regional radiotherapy. The median age at treatment was 55 years (range 28–73) and the median time since treatment was 5 years (range 3–8 years). The concurrent diseases diabetes, rheumatoid arthritis, and stroke were not more frequent in the group with axillary dissection and regional radiotherapy than in the other two groups.

Regional radiotherapy, paraesthesia, and oedema

In the group with axillary dissection and regional radiotherapy 20% reported paraesthesia compared with 13% in the group with axillary dissection only (RR 1.47; 95% CI 1.02–2.11). The corresponding figures for oedema were 22% and 15%, (RR 1.46; 95% CI 1.04–2.03). The relative risk of reporting paraesthesia after radiotherapy becomes 1.28 (95% CI 0.93-1.76) when adjusted for oedema. We found no relation between time since treatment and the occurrence of paraesthesia after regional radiotherapy. More than half (61%) of the women with paraesthesia after axillary dissection and regional radiotherapy reported that this symptom affected their well-being moderately to much. The women with neither axillary dissection nor regional radiotherapy reported the lowest occurrence of paraesthesia 8% and oedema 5%.

Having had mastectomy versus breast conserving surgery did not significantly contribute to paraesthesia (RR 1.13; 95% CI 0.78–1.63). Neither the number of examined axillary lymph nodes (RR 1.02; 95% CI 0.99–1.04) nor having had chemotherapy contributed significantly to paraesthesia (RR 1.29; 95% CI 0.91–1.83). Among the women 49 years of age or younger with axillary dissection and regional radiotherapy, 26.8% reported paraesthesia (RR 2.45; 95% CI 1.05–5.73); among women 50–59 years of age 19.7% reported paraesthesia (RR 1.81; 95% CI 0.73– 4.44), compared with only 10.9% of women over 59 years of age (RR 1.00 Reference) (Figure 11).

Pain and decreased strength

We found no statistically significant differences in reporting pain in the arm, the use of analgesics, or decreased strength between having had both axillary dissection and regional radiotherapy and having had axillary dissection only.

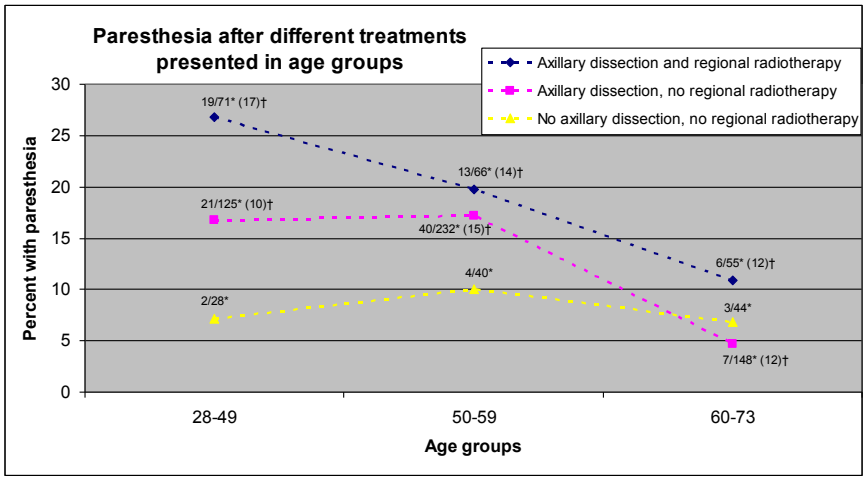


Figure 11: Presenting the percentage of women with paraesthesia in the three different treatment groups as well as in age groups. The women who had regional radiotherapy have a more apparent relation between age and paraesthesia than the women in the other two groups.
*Numbers of women with paraesthesia and the total number of women in each age group.
†The median number of examined lymph nodes is shown within parantheses for each age group.

Paper IV

The following three possible dose-volume predictors were investigated in relation to paraesthesia:

1 – V_{40Gy} (volume), i.e. the delineated volume of the brachial nerve in cm^3 that received at least 40.0 Gy. Due to the relatively large thickness of the CT scanning slices, 5 to 10 mm, we chose to investigate the V_{40Gy} instead of a higher dose that would only have represented a few but highly unreliably cm^3 and thereby would have contributed a large uncertainty concerning the results. The women were divided into three numerically equal groups, < 11.3 cm^3, 11.4 – 13.4 cm^3, and > 13.5 cm^3. Among the women receiving regional radiotherapy with V_{40Gy} >13.5 cm^3 25% reported paraesthesia, resulting in a significantly RR of 1.83 (95% CI 1.13-2.95) (Figure 12). The risk was still significant after adjustment for oedema (RR 1.64; 95% CI 1.12-2.41) (Figure 13). V_{40Gy} below 13.5 cm^3 showed no significant relation to paraesthesia.

2 – The maximum dose within the delineated volume. The calculation grid size was 5x5x5 (- 10) mm (depending on the CT slice thickness), that is different voxels represents different volumes 0.125 or 0.25 cm^3. The women were divided into three groups, < 50.0 Gy, 50.1 – 54.9 Gy, and > 55.0 Gy. Women having maximum dose in plexus brachialis of >55.0 Gy (n=12) had an occurrence of 25% with the highest RR 1.86, however this was not significant and had a wide confidence interval (95% CI 0.68-5.07). The corresponding risk after adjustment for oedema was RR 1.54 (95% CI 0.70-3.40).

3 – The prescribed doses 46 or 50 Gy, to the regional lymph nodes. When evaluating the prescribed doses 46 and 50 Gy, the occurrence of paraesthesia was 21 and 18% with unadjusted RRs of 1.60 (95% CI 1.04-2.44) and 1.34 (95% CI 0.81-2.23). However after adjusting for oedema, it was not significant RR 1.27 (95% CI 0.87-1.83) and RR 1.32 (95% CI 0.85-2.05).

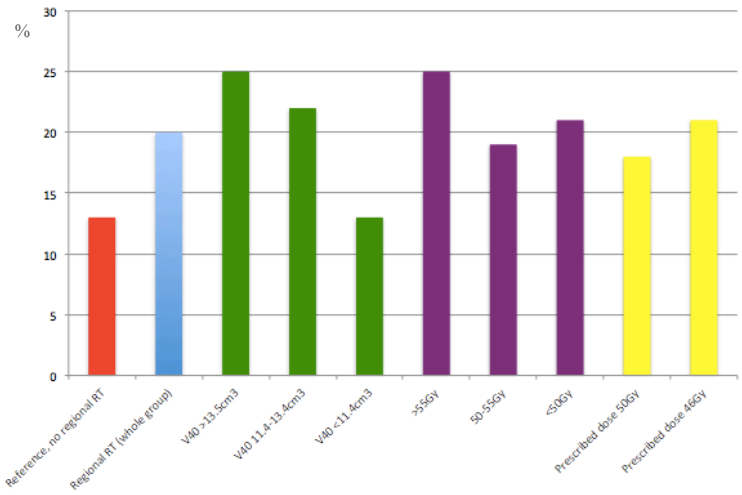


Figure 12: Percent of women reporting paraesthesia in the hand. Presented in subgroups representing various dose-volume aspects.

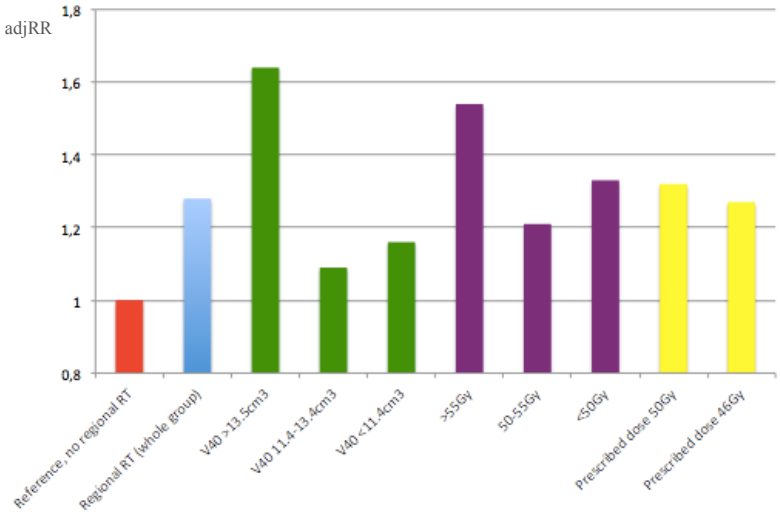
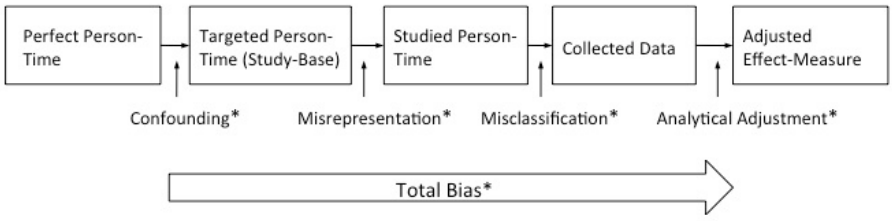


Figure 13: The relative risks of reporting paraesthesia in the hand adjusted for oedema. The women that did not receive regional radiotherapy represent the reference group, 1.00. The subgroups are representing various dose-volume aspects. N.B. the y-axis starts at 0.8.

5 Discussion

5.1 Methodological considerations

In real life it is not possible to carry out an error-free study. All studies include errors, either a systematic error which can introduce bias to the effect-measure, or a random error which can influence the precision of the effect-measure of the study. In our research group, we used epidemiological methods as applied by the hierarchical step-model for causation of bias with the aim of identifying and minimizing the possible sources of bias in the effect-measure in a study [101]. According to the hierarchical step-model, each step of the research process introduces a special source of error. The model depicts how a real-life study (such as ours) deviates from "the perfect study" and proceeds in four steps towards a calculated, often adjusted, effect-measure (Figure 14).



Figur 14: The hierachical step-model for causation of bias. * Total bias from the perfect person time to the adjusted effect-measure.

Step 1: Confounding

A confounding factor may produce a spurious association between the studied variables when no real association between them exists. If confounding factors are neither measured nor considered, results may be biased. To be defined as a confounding factor, the factor must be both associated with the exposure (in our study, radiotherapy) and be an independent risk factor for the outcome (in our study, long-term symptom).

When confounding factors are not taken into account, the effect-measure may over or under estimate the true association between exposure and outcome.

In our study, preventative measures were taken in the preparatory phase to avoid systematic errors due to confounding factors. Since breast cancer is much more common among women than among men, we focused only on the women and we did therefore not have to take gender into account as a possible confounder. We excluded women with cancer recurrences since this could cause e.g. pain or neuropathy. We collected as much information as possible on other confounding factors, either through the questionnaires of through medical records. Information assessed from cancer survivors included; age, education, smoking, BMI, medications, marital status, parity, co-morbidities such as diabetes mellitus, neurological diseases, cardiovascular diseases (e.g. stroke, hypertension, ischemic heart disease). From medical records we collected data on diagnosis, stage of disease, treatment modality, recurrence and radiotherapy doses. Known or suspected causal factors for the outcome studied were taken into account in our analyses.

Step 2: Misrepresentation

In the second step of the hierarchical step-model, bias due to non-representation and selection-introduced problems is introduced, since this reveals a difference between the targeted person-time and the observed person-time. The study was well grounded in the initial qualitative phase with validation of the instrument and the method being tested in a pilot study within the study-population to make sure that we could continue to the quantitative phase and collect data.

Non-participants induce loss of information from the targeted person-time and therefore it is crucial to avoid non-participation. The participation rate was assessed in a pilot study before moving on to the main study. The participation rate in the pilot and main studies was high, 94, 85 and 85 percent respectively for the pilot, cohort 1 and 2. A description of our method of collection data, including an informative introduction letter sent to all participants and following introductory telephone call, has been described in the chapter on Method. We believe that working intensely in the initial phase of data collection can partly explain our reasonably high participation rate, thereby minimizing risk of selection-induced problems.

We can only speculate if non-participants for whom we have no information belong to the healthier part of the population or the less healthy. We cannot

overrule the possibility that those who did not participate were somehow different than participants which might influence our results.

Step 3: Misclassification

According to the hierarchical step-model for causation of bias, the third step of a study may introduce bias when the information collected is incorrect for some reason. Therefore, an important part of each study is the instrument. In developing our instrument, we began by performing semi-structured interviews with the target population (breast cancer survivors). During the interviews they were all given the chance to talk about their personal experience and the challenge that can arise in their new life situation after a cancer treatment. The interviews proceeded with additional cancer survivors until we did not gain any new information (saturation). The development of the study-specific questionnaire was therefore founded in the interviews, our clinical knowledge and in the literature.

An important task was to make all questions clear and understandable. Face-to-face validation within the study-population led to modifications, new drafts were developed and validated. We believe that by intensively preparing the questionnaire and developing questions with the studied population in a face-to-face situation we increase the likelihood of the respondents acknowledging the questions and answering them as intended, thereby decreasing the risk of misclassification.

The questionnaire was mailed to the participants. They had several weeks to complete the questionnaire in the privacy and security of their own home. We believe that this lowers the risk of potential interviewer-induced bias. The researchers were also independent from a clinical setting, which decreases the risk of "I-want-to-please-my-radiotherapist" bias.

Step 4: Analytical adjustment

Statistics are used to estimate effects of an association. Errors may occur due to confounders and other biases. In the ideal study the two categories of exposure (women receiving radiotherapy treatment or not) are supposed to resemble each other as much as possible (for example age and systemic treatment). In order to imitate the role model of studies – randomisation – and to make the comparison between the groups as perfect as possible we adjusted for possible risk factors as e.g. age and chemotherapy. Furthermore, to reduce the risk of significance due to a high number of questions in our questionnaire we pre-specified our hypothesis. We used relative risks as an

effect measure in many of the analyses since we believe that this is an understandable way of illustrating the clinical effect of a certain treatment for a clinician.

5.2 General discussion

To compare the occurrence of symptoms (late side-effects) 10 to 17 years after breast irradiation we used a cohort of women who were randomised to receive tangential breast irradiation or not after breast conserving surgery with axillary dissection due to breast cancer.

We showed that the radiotherapy group did report breast pain and disturbances of skin sensation after radiotherapy significantly more often than those in the non-radiotherapy group. Even though the women who received radiotherapy in our study reported a higher occurrence of breast pain of any degree of severity, they did not report a statistically significant higher occurrence of the subcategory severe breast pain or a higher consumption of analgesics. When we asked about self-assessed quality of life there were no differences between the groups for problems in daily life related to pain or for quality of life.

Pain in the breast area as a late adverse effect due to breast surgery with or without radiotherapy is previously known [105]. The background is not completely understood. Axillary dissection can injure the intercostobrachial nerve and cause pain. However, only 0.6% in the group with axillary dissection had breast pain compared to 8.8% in the group with both axillary dissection and radiotherapy of the breast, thus radiotherapy seems to be the main cause of this effect. Langer *et al.* [106] found that breast pain was equally common approximately 2.5 years after breast conserving surgery with sentinel node and radiotherapy compared to breast conserving surgery with axillary dissection and radiotherapy which also indicates that there is an alternative origin to pain besides the intercostobrachial nerve. Another known cause of chronic pain and severe mechanosensitivity is neuromas that can form whenever peripheral nerves are injured, as in scar tissues [107]. And in contrast to normal wound healing, we know that radiotherapy can prolong the fibrogenic process for a substantial time due to activated cytokines and growth factors [59, 108]. Possibly radiotherapy could affect the origination of neuromas and be a part in the complex pathophysiology. Regarding affected skin sensitivity we found that hypersensitivity is reported significantly more often in the radiotherapy group. Tasmuth *et al* [109] found a significantly

higher prevalence of paraesthesia in the breast-conserving group with radiotherapy compared to the mastectomy group without radiotherapy. Ververs et al found as well a more sensitive scar in women who underwent irradiation of the breast or chest wall compared to the women who did not receive radiotherapy [110]. Questions from women receiving radiotherapy about sensitivity to sun exposure are common issues in the daily work at the oncology department. We have not found any publications regarding this subject. Seven percent of the irradiated women report higher sensitivity to sun exposure if they compare to their contra lateral breast, and it affected the wellbeing in the radiotherapy group. The mechanisms behind these symptoms could be atrophy and fibrosis, that is well known late changes in the skin [111, 112] together with neuromas as described above.

The occurrence of self reported oedema in breast or arm, erysipelas, heart symptoms, lung symptoms, rib fractures, and decreased shoulder mobility in women with breast cancer treated with breast-conserving surgery and postoperative radiotherapy was similar to that in women who had surgery only.

We found no difference between the two groups regarding cardiovascular symptoms. To properly evaluate cardiotoxicity a greater number of patients and a longer follow-up time are probably needed. The cardiovascular effect of modern radiotherapy from the 1990s onward seems to have diminished with individual dose planning but that may also be explained by shorter follow-up [42]. Moreover, the risk of cardiovascular disease increases with radiotherapy to the internal mammary chains but these lymph nodes were not targeted in the women we have investigated [71].

We proceeded in the research leading to the second article with a search for patient and treatment-related risk factors of developing long-lasting breast pain after breast cancer radiotherapy. Younger women who have undergone breast-conserving surgery with postoperative radiotherapy reported a higher occurrence of long-lasting breast pain compared with older women. In agreement with our study, previous studies have shown that age is an effect-modifier and that younger women have a higher occurrence of pain after breast cancer treatment with or without radiotherapy than older women [80, 105]. There is probably a combination of biology and psychology behind the age-related pain occurrence. Our findings are in contrast to the general Swedish female population where the general mean pain score increases with age, indicating that breast pain among young women is treatment related [113]. We also found that time since treatment decreases the frequency of

occurrence of pain. In the literature, some report a pain decrease over time [78, 114] whereas others report no relation to time elapsed [79, 115].

The translation of the questions in the questionnaire before publication could initiate interpretation difficulties due to the complexity with both linguistic and cultural aspects. For example, in the Swedish questionnaire we used the phrase "ömhet i bröstet" and we used these words because this was a common phrase applied by the women during the interviews. The original question in the Swedish questionnaire was: "Har du känt ömhet i vänster/höger bröst det senaste halvåret?". The answer category was: "Nej", "Ja, vid enstaka tillfällen", "Ja, åtminstone någon gång varje månad", "Ja, åtminstone någon gång varje vecka", "Ja, åtminstone tre gånger varje vecka", "Ja, åtminstone någon gång varje dag". When we made the translation we considered that the most appropriate English word in this context was pain. The occurrence of breast pain was lower or similar (5% and 13% in paper I and II) to others (15 to 73%) that asked about pain after breast cancer treatment in the literature [77, 78, 105, 114-116]. Whelan *et al* [114] investigated an English-speaking population and reported that 15% of the patients reported breast pain. In the START trials [117] pain in the breast area was reported by 20 to 23 % of the British women. Furthermore, in paper II we reported that women that had breast pain consumed analgesics every week significantly more often than the women without pain, 30.4% vs. 8.6% (RR 3.54; 95% CI 2.47-5.09), see page 32. Therefore we do not believe that we have made an overestimation of the symptom in the English version.

We found a significantly higher occurrence of paraesthesia after axillary dissection and regional radiotherapy than after axillary dissection without regional radiotherapy in paper III. There were no significant differences in pain or in decreased strength between the different treatments. The women with neither axillary dissection nor regional radiotherapy reported the lowest occurrence of symptoms. We had no relation between the occurrence of paraesthesia and time after treatment in our cross-sectional study. Bajrovic *et al*. [118] presented an increase in the prevalence of neuropathy prevalence over time, 3.9% after 5 years and 24.5% after 10 years among women treated for breast cancer who received a total dose of 60 Gy with 3 Gy per fraction to the supraclavicular lymph nodes. In our study we used three-dimensional dose planning, a lower radiotherapy dose per fractionation, and a lower total dose, which could explain why we did not find any increase in prevalence of paraesthesia over time. This could also explain why we did not find any increased occurrence of pain or neurological motor deficits in the arm and hand after regional radiotherapy. The interval between treatment and symptoms probably depends on the total dose and the dose per fraction [119,

120]. A short follow-up time may underestimate the final occurrence of neuropathy and our follow-up of three to eight years could be too short to distinguish the occurrence of symptoms over time [118, 121]. However, Fathers *et al.* reported in 2002 that most patients developed their symptoms of neuropathy within three years, but some after eight years [122].

In addition to the paraesthesia we found a significantly higher occurrence of oedema after axillary dissection and regional radiotherapy than without regional radiotherapy. There is a strong relation between regional radiotherapy, oedema, and paraesthesia that makes it difficult to distinguish the causal factors of the paraesthesia. More than half of the women with paraesthesia after regional radiotherapy also had oedema. When adjusted for oedema the contribution from radiotherapy is no longer formally statistically significant. Therefore, we conclude that regional radiotherapy increases the risk of paraesthesia, however it can be mediated either directly by the plexus brachial nerve, indirectly via oedema, or in combination.

Paraesthesia is a rather common symptom among the Swedish female population with a prevalence of approximately 17%, where e.g. carpal tunnel syndrome is represented by 5 % [123]. In our study we used the women that did not have axillary dissection as a reference for paraesthesia (8 %). To quantify the neuropathy in detail we would need to perform a clinical neurological and physiological examination including an electromyographic investigation (EMG) of the patients [124, 125]. However, since that approach was not part of this work the cause-effect must be interpreted with caution. We adjusted for having paraesthesia after regional radiotherapy with oedema. This resulted in the conclusion that the regional radiotherapy still numerically increased the risk of reporting paraesthesia but without statistical significance, RR 1.28 (95% CI 0.93-1.76). To better understand the relation between the regional radiotherapy (exposure) and paraesthesia (effect) we increased the precision of the exposure variable by doing a dose-volume response analysis with a delineation of the brachial nerve on the dose planning CT. Instead of only comparing regional radiotherapy or not we investigated; brachial nerve volume receiving 40 Gy or more (V_{40Gy}), maximum dose in the brachial nerve, and prescribed regional dose. We found that among the women receiving regional radiotherapy with V_{40Gy} >13.5 cm^3 25% reported paraesthesia, resulting in a significantly RR of 1.83 (95% CI 1.13-2.95). The risk was still significant after adjustment for oedema (RR 1.64; 95% CI 1.12-2.41).

Our delineation of the brachial nerve is afflicted with several limitations. The main limitation is that the brachial nerve is not visible on the noncontrast CT;

the delineation is made indirectly guided by the borders of the surrounding tissues. However, as the brachial nerve passes right through the PTV we know that at least some volume receives the prescribed dose. Another limitation is the thickness of the CT scanning slices, 5 to 10 mm, which results in low precision of the estimated dose variable in the organ at risk. Furthermore, the anatomic normal variation of the brachial nerves is not possible to detect on the CT-scan [126]. Future studies in this field with regional radiotherapy due to breast cancer should delineate the brachial nerve as an organ-at-risk on magnetic resonance imaging (MRI), as has been proposed by Platteaux *et al* for radiotherapy due to head and neck cancer [127].

It is well known that higher doses to the brachial nerve increase the risk of neuropathy; this has been shown by e.g. Powell [128], Olsen [125], and Johansson [129] when they compared different fractionation schedules. However, this is the first attempt to delineate the brachial nerve and search for a link between dose-volume and long-term symptoms after modern breast cancer radiotherapy. A small volume effect was also suggested by Emami *et al* [91] when they divided the brachial nerve into thirds, where irradiation of one third is a little more radioresistant than irradiation of all three thirds at the same time. Our results indicate that larger volumes of irradiation of $\geq$40 Gy to the brachial nerve seem to increase the occurrence of long-term paraesthesia. However, the results must be interpreted with caution. Further studies with higher precision in the delineation of the brachial nerve and with wider range of dose exposure are needed.

6 CONCLUSION

The conclusions from our study regarding long-terms symptoms after external breast cancer radiotherapy are:

- Postoperative radiotherapy to the breast after breast-conserving surgery increases the risk of long-term breast pain.
- Young women, below 50 years of age, have a higher risk of having breast pain after radiotherapy than older women.
- The majority of the women have no or minor additional long-term symptoms after breast cancer radiotherapy compared to breast-conserving surgery only.
- The addition of radiotherapy to the regional lymph nodes increases the risk of paraesthesia in the hand.

7 Future perspectives

One way to reduce the side effects would be to reduce the irradiated volume of normal tissue [130]. However, this must be done without compromising the dose to the tumour cells. Since most local recurrences in the breast occur near the lumpectomy site [25], studies on partial breast irradiation is on-going as an alternative to the standard whole breast irradiation for selected groups, thereby reducing the volume of irradiated normal tissue (e.g. the breast, the lung, the heart). Methods of partial breast irradiation are e.g. brachytherapy (e.g. Mammosite – balloon intracavitary brachytherapy) [131, 132], IMRT (intensity-modulated radiation therapy) [133-135], and intraoperative radiotherapy [136, 137]. These radiotherapy techniques are often referred to as accelerated partial breast irradiation (APBI) since they also are hypofractionated. Results from these on-going randomised APBI-studies are expected relatively soon and may change the praxis for part of the breast cancer radiotherapy [138]. Breathing adapted radiotherapy (gating technique) [135, 139, 140] is another possible treatment modality and it aims to reduce the irradiated volume of normal tissue in the heart by increasing the space between the breast and the heart.

The development of the image technologies; from x-ray to computed tomography (CT) and further to magnetic resonance imaging (MRI) and positron emission tomography (PET) [141] enhances the possibility for the physician to identify the target and thereby reduce the depicted extra margin volume in the normal tissue.

When we better understand the relation between the tumour biology and patterns of recurrences we can treat patients with high risk and exclude treatment when the benefit of radiotherapy is expected to be very limited. This might be made possible by using gene expression profiling which has presented molecular subtypes based on similarities in gene expression: luminal A, luminal B, HER2 overexpressing (non luminal), and basal-like. Should all these breast cancer subtypes be treated equally or should we give hypofractionation, APBI, or even exclude the irradiation of women with a certain subtype? [46, 142, 143] The knowledge of “minor” radiotherapy side effects becomes more important when balancing the scale between pros and cons when we become able to predict subgroups with very limited gain from post-operative breast radiotherapy.

”Forewarned, forearmed; to be prepared is half the victory’’ said Miguel de Cervantes, author of the novel Don Quixote [144]. If we cannot avoid the side effects we need to present adequate information to the women. By informing the patients before the treatment and thereby make her a part of the planned treatment it will be easier to cope with possible side effects, i.e. enhance her preparedness.

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