IMMEDIATE BREAST RECONSTRUCTION WITH A SUBPECTORALLY PLACED SILICONE PROSTHESIS

RHEUMATOLOGICAL, PSYCHOLOGICAL AND CLINICAL ASPECTS

C.M.E. Contant

Immediate breast reconstruction with a subpectorally placed silicone prosthesis
rheumatological, psychological and clinical aspects

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Financial support for the printing of this thesis was obtained by kind contributions from
Mentor Benelux BV, Leiden
Pharmachemie BV, Haarlem
Emdaplast BV, Zoetermeer
Novartis Pharma BV, Arnhem
Johnson and Johnson Medical BV (divisie breastcare), Amersfoort

Cover
"Tip toe", Wies van Dort, photographed by
Robbert Peek, Fotografie, Rotterdam

Printed by Optima Grafische Communicatie, Rotterdam

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Directe borst reconstructie met een subpectoraal geplaatste siliconen prothese
reumatologische, psychologische en klinische aspecten

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus

Prof.dr.ir. J.H. van Bemmel

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 16 april 2003 om 9.45 uur

door

Cornelia Maria Elisabeth Contant

geboren te Hazerswoude

Promotiecommissie

Promotor:
Prof.dr. A.M.M. Eggermont

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"and when old words die out on the tongue, new melodie break forth from the heart; and where old tracks are lost, new country is revealed with its wonders"

Rabindranath Tagore, 'Gitanjali'
(by Nelke Manders)

CHAPTER I

Introduction

INTRODUCTION

Breast cancer is the most frequently diagnosed solid tumour in women in the western world. In the Netherlands, breast cancer affects about 1.2 per 1000 women a year. At present about 10% of all Dutch women develop breast cancer in the course of their life, of whom approximately 80% are under the age of 65 years.[1]

1.1 HISTORICAL NOTES ON THE TREATMENT OF BREAST CANCER

Before the second half of the 19th century breast cancer was treated surgically only when it had reached its advanced stage of a bulky, ulcerating and often painful mass, mostly uncontrollable locally and almost inevitably leading to death. Better understanding of tumour biology, based on anatomical studies of the breast and its lymphatics, was required to recognise tumours in the breast at an earlier, possibly curable, stage of breast cancer.[2] The development of antisepsis and anaesthesia made it possible to perform the operations, for which a rationale based on early detection was set up.

The 'Halstedian concept', which implied that breast cancer disseminates by infiltration into the surrounding tissues and in a stepwise manner affects the regional lymph nodes, had dominated all theories of breast cancer treatment for many decades until the present day. Based on this concept, Halsted introduced the radical mastectomy, which entailed removal of both pectoral muscles en bloc with the breast as well as the axillary and in later years also the supraclavicular lymph nodes. At the end of the 19th century, Meyer[3] and Halsted[4] reported better results of survival and, above all, a much better local tumour control by achieving more radical surgery for early breast cancer than was considered acceptable until then. The en bloc approach of the diseased organ, with its regional lymph nodes, became the guiding principle in cancer surgery.

In the middle of the 20th century Patey[5] and Madden[6] introduced less mutilating surgery, with preservation of the pectoralis muscles. The 'modified radical mastectomy' was found to be equally effective as radical mastectomy with regard to locoregional control and survival, and became the standard technique for the surgical treatment of breast cancer.[7,8] With tumour detection still relying solely on clinical examination, the mammography (introduced in 1956) offered a valuable method to detect smaller, non-palpable breast tumours.[9] As a result, surgeons were more frequently confronted with minimal cancers and the discussion arose as to whether a mutilating procedure could be avoided.[10] Various institutes developed schedules for breast conserving therapy (BCT), which implied wide tumourectomy and axillary clearance followed by whole breast irradiation and a boost irradiation to the original tumour bed. Several prospective randomised trials demonstrated the equivalance of BCT and modified radical mastectomy for both local control and survival rates.[11-16] Nowadays, BCT is widely embraced

as an acceptable standard of care in the management of breast cancer.[17] However, BCT is not recommended for all patients. Depending on size in relation to the breast or pathological features of the tumour, mastectomy may be preferable. In these cases, breast reconstruction may be the means to improve cosmesis.

Recent advances associated in genetic testing have allowed to identify women at increased risk of breast cancer. These women are members of a hereditary breast (and ovarian) cancer (HB(O)C) family or carry a mutation in either the BRCA1 or BRCA2 gene. Regular surveillance, chemoprevention or prophylactic bilateral mastectomy are options that are discussed with women at increased risk of breast cancer. In case of a prophylactic mastectomy women can be offered breast reconstruction.

I.2 BREAST RECONSTRUCTION

Breast reconstruction has undergone tremendous evolution in the last 30 years and continues to evolve from year to year.[18] Current methods of reconstruction can be broadly classified into autologous tissue in which patient's own tissue (skin, subcutaneous tissue and muscle) is used and the use of prosthetic material (silicone or saline-filled implants).

Before the availability of myocutaneous flaps, a limited amount of reconstructions was performed with local skin flaps, e.g. contralateral breast sharing. Silicone gel implants were introduced in the late 1960s. They were first used alone as a single-stage procedure and their appliance was severely limited by deficient tissue coverage. Later, combined with latissimus dorsi myocutaneous flaps in delayed reconstruction, they achieved greater success. With the development of tissue expanders in the 1970s, limitation of skin became less of an issue, and tissue expansion with a second-stage replacement for a silicone prosthesis became a popular technique. In 1992, the U.S. Food and Drug Administration (FDA) placed a moratorium on the use of silicone gel implants because of concern about the development of rheumatic disorders. The FDA decided to allow the use of silicone implants under controlled situations only.[19] To date there is no convincing cause and effect between 'human adjuvant disease' and the use of silicone gel implants.[20] However, since that time, saline implants have become more popular for implant reconstruction. Expander and implant reconstruction continues to be the most widely used form of reconstruction.[18] In recent years improved autogenous reconstructive techniques, such as the latissimus dorsi myocutaneous flap, the (free or pedicled) transverse rectus abdominis myocutaneous flap, the deep inferior epigastric artery perforator flap, or the free superior gluteal artery perforator flap, have led to an increase in flap reconstruction.

Breast reconstruction can either be performed as a separate procedure (delayed reconstruction) or at the time of the initial mastectomy (immediate reconstruction). Historically, there was concern that immediate breast reconstruction may compromise not only the effectiveness of cancer surgery (e.g. delaying adjuvant therapy), but that it may also impair

detection of local recurrences. The other main argument against immediate reconstruction was the concern that women would not be able to accept the change in their breast from normal to reconstructed breast, whereas they would be able to accept the change from nothing to a reconstructed breast. Therefore, the traditional concept of performing a breast reconstruction was done after mastectomy as a separate procedure after the completion of systemic therapy and healing. However, as reconstruction techniques evolved, the challenge to ensure continued safety and efficacy after immediate breast reconstruction was addressed by several groups.[21-24] Moreover, immediate breast reconstruction was found not to interfere with adjuvant systemic therapy.[25]

Immediate breast reconstruction has several advantages over delayed reconstruction. Because mastectomy and reconstruction are performed in one stage, the total hospital costs and convalescent time are reduced compared with mastectomy and delayed reconstruction.[26] It also spares women the psychological trauma of living with deformity.[27,28] Moreover, critical landmarks for optimising breast form and symmetry are the inframammary fold and the breast skin envelope, both of which can be preserved and maintained in their native state with immediate breast reconstruction.

In 1990 the Department of Surgical Oncology at the Erasmus Medical Centre/Daniel den Hoed Cancer Centre, introduced immediate breast reconstruction with a subpectorally placed silicone prosthesis after mastectomy for breast cancer or after prophylactic mastectomy. The rationale for choosing this type of immediate reconstruction was the relatively simple technique, and the relatively short operation time. Furthermore, subpectoral insertion of the prosthesis offers the same oncological screening as with regular mastectomy. Theoretically, a local recurrence could be detected by palpation of the chest wall and is not masked by a musculocutaneous flap which is positioned on the pectoral muscles.

In 1995 a working group was set up in our centre consisting of an oncological surgeon (AN van Geel), a plastic surgeon (R Tjong Joe Wai), a health psychologist (AME van Wersch), a radiologist (AIM Obdeyn) and a rheumatologist (AJG Swaak). Using a well-defined protocol, their aim was to follow every woman who underwent an immediate breast reconstruction with a subpectorally placed silicone prosthesis. They formulated a number of questions about immediate breast reconstruction and silicone prosthesis; these questions are addressed in this thesis.

I.3 OUTLINE OF THE THESIS

Chapter 2 explores the possible association between silicone breast implants and the existence of a silicone-related symptom complex (SRSC). In a retrospective study the relation between SRSC and expression of antinuclear antibodies (ANA) in the serum of women with silicone

implants was evaluated (chapter II.1). Since 1995 all women who underwent immediate breast reconstruction with a subpectorally placed silicone prosthesis have been tested for the presence of ANA as well as completing of a questionnaire dealing with SRSC. In chapter II.2 we examine the prevalence of symptoms related to SRSC, the prevalence of ANA, and whether a relationship exists between SRSC, ANA and implant integrity one year after silicone breast implantation. Based on the results of this study, the follow-up was prolonged and all women were evaluated a second time, both serologically (ANA) and by questionnaire (SRSC), minimally 3 years after implantation of the silicone prosthesis (chapter II.3).

Chapter 3 addresses the psychological aspects of immediate breast reconstruction (IBR) with a subpectorally placed silicone prosthesis. In chapter III.1 the patient's motivation for and satisfaction with both the treatment and information received of IBR are described. Satisfaction was more deeply studied by relating it to the quality of life, body image and sexual functioning. In 1995 a new study was initiated to review the effects of this treatment with the aim to evaluate the satisfaction with IBR one year after operation. Special attention is paid to the differences in satisfaction, and specific prosthesis-related complaints of IBR between the different operation indications, i.e. after prophylactic or oncological mastectomy (chapter III.2).

Chapter 4 evaluates clinical aspects of IBR with a subpectorally placed silicone prosthesis, focusing on morbidity of this procedure, the effect of radiotherapy before and after IBR (chapter IV.1), and the inverted drip incision (chapter IV.2). Chapter IV.3 describes the management of women who have chosen to undergo prophylactic mastectomy (PM), mostly in combination with IBR; the preliminary results of oncological follow-up after PM are also reported. Chapter IV.4 discusses the detection of local regional recurrence (LRR), i.e. ipsilateral chest wall recurrence or ipsilateral axillary recurrence, after mastectomy followed by IBR. Special attention is paid to clinical, surgical and pathological features in relation to the appearance of LRR of breast cancer after SSM and IBR.

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CHAPTER II.1

First evaluation study on the Rotterdam working party on silicone breast implants (SBI) and the silicone-related symptom complex (SRSC)

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R Tjong Joe Wai, and AN van Geel

Clinical Rheumatology 2000;19:458-463

ABSTRACT

Objective: This cohort study evaluates the postoperative prevalence of antinuclear antibodies (ANA) in relation to symptoms related to the so-called silicone-related symptom complex (SRSC).

Methods: A total of 63 women who underwent mastectomy followed by immediate breast reconstruction with a silicone breast implant (SBI) between September 1990 and May 1995 at the University Hospital Rotterdam/Daniel den Hoed Cancer Centre, participated voluntary in the study. Their sera were tested for the presence of ANA and at the same time they were screened for the prevalence of SRSC-related symptoms by questionnaire

Results: Sixteen percent of the women were ANA positive. There was no difference in SRSC expression between ANA-positive and ANA-negative women.

Conclusions: The lack of difference in symptom expression between the ANA-positive and ANA-negative women and the rather low complaint percentage proves that if ANA positivity is related to the SRSC, we found no evidence that patients with a SBI with a positive ANA differed from the ANA-negative patients.

INTRODUCTION

Since 1962 silicone breast implants have become widely used for both cosmetic and reconstructive surgery.[1] After its introduction, it was claimed that silicone could induce connective tissue disease (CTD)[2,3,4]. Other syndromes, such as scleroderma[5-10] or rheumatoid arthritis (RA)[11] have also been documented.These observations were generated from descriptive uncontrolled studies and case reports. In 1988 the first cohort study was published by Weisman et al.[12], who could show no association between silicone breast prosthesis and RA and/or CTD. Since then more studies have followed reporting evidence for neither RA nor CTD[13-18] nor scleroderma[17,19,20] as an increased risk in patients with breast implants. However, some authors have continued to suggest the occurrence of atypical connective tissue diseases[21-23] defined by fatigue, myalgias and arthralgias or atypical rheumatic disorder[24-26] which includes arthralgia, myalgia, sicca complex, paraesthesiae, balance disturbance, night sweats, rashes, memory difficulty and fatigue in patients with silicone breast implants (SBI).

In recent studies it was hypothized that silicone could induce an autoimmune response. Elevated levels of anticollagen autoantibodies were reported in women with silicone implants.[27,28]

Recently raised titers of ANA have been found in patients with silicone breast implants.[22,23,26] All these studies included women with silicone prosthesis and medical complaints related to the silicone-related symptom complex (SRSC).

Until now no prospective (longitudinal) studies have been available in which patients with an SBI were followed in order to investigate the eventual development of the so-called SRSC and the development of ANA. In 1995 a working party was set up in the Netherlands to begin a prospective longitudinal study to follow from that moment on every patient who underwent a reconstructive breast operation with a silicone prosthesis, according to a define protocol. Because silicone prosthese for immediate breast reconstruction after mastectomy were introduced in our department from 1990 on, all patients who were operated on between 1990 and 1995 were included in this cohort study. For this investigation a protocol was developed containing a questionnaire, clinical signs obtained by physical examination, and sera taken for the detection of autoantibodies. The aim of this first evaluation study was to report the prevalence of symptoms in a patient cohort having had a breast reconstruction operation with silicone implant, related to the SRSC, the prevalence of ANA, and to study whether a relationship can be established between the two.

PATIENTS AND METHODS

Between September 1990 and May 1995 102 women underwent mastectomy followed by immediate breast reconstruction with a subpectoral placed silicone prosthesis. A general

surgeon and a plastic surgeon at the University Hospital Rotterdam/Daniel den Hoed Clinic carried out all operations. The sera obtained from these patients were tested for the presence of antinuclear antibodies (ANA) using the immunofluorence assay on HEP-2 cells at the Department of Autoimmune Disease (CLB), Amsterdam. For women with bilateral reconstruction the earliest date of surgery was considered. Together with the blood samples the women were asked to complete a questionnaire, the aim of which was to make an inventory of type of complaints that are mostly reported on SRSC. The complaints were ordered in such a way that insight was also obtained about eventual specificity for a defined disease. But the questionnaire was not designed to establish a diagnosis. There were specific questions related to symptoms referable to 1) Sjögren's syndrome, such as keratoconjunctivitis sicca: a dry, burning, sore, red, gritty feeling and photosensitivity, and/or xerostomia: dry, difficulty when eating dry food, the need of water at bedside/at dinner, sucking a sweet; 2) rheumatoid arthritis: swollen, painful and stiff joints; 3) Raynaud's phenomenon; and 4) undefined complaints, such as headache, dizziness, palpitations, sweating and diarrhoea. The maximal score for Sjögren-related symptoms is 12, for rheumatoid arthritis and Raynaud's phenomenon is 4, and for undefined complaints 5.

From 63 women both sera and completed questionnaire were obtained. These patients were included in this study. Of the other 39 patients incomplete data were obtained and some patients were lost for follow up. Participation in this study was voluntary at any time after surgery and was asked about during follow-up at the outpatient clinic.

Statistical Analysis

Fisher's exact test was used for the statistical calculations. Differences between observed groups were considered statistically significant with P values <0.05.

RESULTS

Fifty-three women underwent unilateral and 10 underwent bilateral mastectomy, resulting in 73 immediate breast reconstructions with silicone implants. The indications for mastectomy were breast cancer (42), extensive ductal carcinoma in situ (21), prophylactic ablatio mammae (8) and Paget's disease (2). The mean age at operation was 46 years (SD 9 years, range 25-71 years, median 46 years). The mean patient age at ANA-testing was 48 years (SD 8 years, median 47 years), with a range of 33 to 72 years. The characteristics are summerised in Table 1.

ANA Positivity

Ten of the 63 patients (15.8%) with silicone prosthesis are positive for ANA. Time from silicone implantation to ANA screening ranged from 2 months to 16,3 years (median 15,3 months). ANA positivity was found 2-29 months after implantation.

Table 1. Characteristics of women with silicone breast reconstruction (n=63)

Mean age at operation	46 years
Mean age at ANA testing	48 years
Indications for mastectomy	
Breast cancer	42
DCIS	21
Prophylactic	8
Paget's disease	2
Total number of breast reconstruction	73

Table 2. Complaints of the women with silicone breast reconstruction (n=63)

Complaints	answered positively (%)
Sjögren	
Eyes:	
Dry	11
Sore	14
Burning	22
Gritty feeling	14
Red	8
Inflammation	6
Sun sensitivity	14
Mouth:	
Dry	22
Difficulty when eating dry food	-
In the need of H_2O at dinner	6
In the need of H_2O at bedside	14
Sucking a sweet	13
RA/Reynaud:	
Cold fingers/toes	33
Joints:	
Stiffness	48
Painful	35
Swollen	8
Undefined complaints:	
Headache	32
Dizziness	25
Palpitations	24
Diarrhoea	8
Transpiration	43

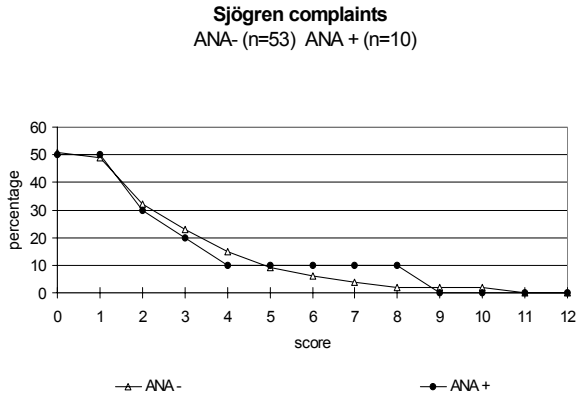

Figure 1. Sjögren complaints (maximum score 12)

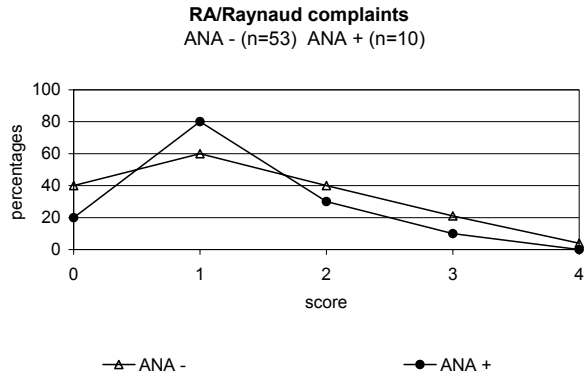

Figure 2. Rheumatoid arthritis/Raynaud complaints (maximum score 4)

ANA Positivity in Relation to Rheumatic Disease-Related Symptoms

The maximal score for Sjögren related symptoms is 12, but none of the women in the ANA-positive or ANA-negative group had such a score. In each group 50% of the women had one or more symptoms.(Table 2) Only 6 women answered five or more Sjögren-related questions positively (5 [11%] were ANA negative and 1 [10%] was ANA positive) (Fig.1). Two women had the maximum score for 4 in the RA/Raynaud related symptoms and were ANA negative. However, women who were ANA positive had more RA/Raynaud related complaints (one or more symptoms 80% and 60%, ANA positive and ANA negative respectively) (Fig. 2). Within the undefined complaints related group there were as many women who had one or more symptoms as those without complaints for both ANA-positive (50%) and ANA-negative (55%) groups (Fig. 3).

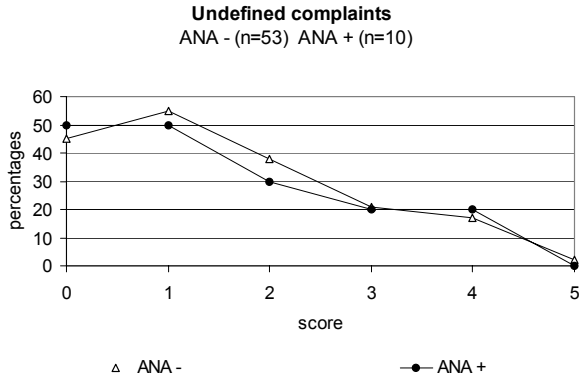

Figure 3. Undefined complaints (maximum score 5)

DISCUSSION

'The silicone breast implant (SBI) controversy continues'. With this sentence a recent editorial began, claiming that according to the observations by these authors a relationship could still exist between silicone implants and a so-called 'silicone-related symptom complex'.[29] On analysing the editorial it was very surprising to find that all arguments were based on circumstantial evidence, i.e. patients improved overall when their implants were removed. The authors clearly described their belief as stated. In the editorial no references were made to studies that are currently available, however retrospective in nature but still proving that no silicone-related symptom complex exists.

In a second editorial in the same journal[30] a conclusion was reached that the only way to obtain an answer to the question as to whether SBI actually causes disease(s), is to follow patients prospectively. In order to investigate the relationship between SBI and the

Table 3. Symptoms and ANA positivity in women with silione breast implants (percentages)

	Freundlich[22]	Vasey[23]	Solomon[26]	Borenstein[35]	Contant
N	50	50	176	100	63
ANA	20	26	25	26	16
Stiff joints	-	-	-	-	48
Painful joints	-	60	56	69	35
Swollen joints	42	42	-	-	8
Raynaud	35	14	24	8	33
Myalgia	-	84	24	62	-
Dry mouth	52	10	53	-	22
Dry eyes	54	14	50	-	11

Table4.Differencesinrating-scalebetweenANA+andANA-groupswithinthereconstructedgroup(n=63)(cumulative)

Scale	score	ANA - (n=53)	ANA + (n=10)
Sjögren	12	0	0
	11	0	0
	10	1	0
	9	1	0
	8	1	1
	7	2	1
	6	3	1
	5	5	1
	4	8	1
	3	12	2
	2	17	3
	1	26	5
	0	27	5
RA/Raynaud	4	2	0
	3	11	1
	2	21	3
	1	32	8
	0	21	2
Undefined complaints	5	1	0
	4	9	2
	3	11	2
	2	20	3
	1	29	5
	0	24	5

development of a SRSC different studies have been performed. Many describes the symptoms of patients with an SBI, and what happened to them when the SBI were removed. All these studies were highly suggestive that a relationship may exist. However, no increased incidence of SBI could be reported in patient groups with defined CTD.[31,32] The intention of our study was to investigate complaints related to SRSC, and to study the prevalence of ANA in SBI patients who were recently operated on at our institute. A drawback of our study is that all parameters were obtained after surgery, and it is possible that some patients were already ANA positive at the time. The aim of our investigation was still to study whether a difference exists between ANA-positive and/or -negative SBI patients in regard to SRSC.

Less than 20% of our patients had complaints of dry, sore, or red eyes, a gritty feeling, inflammation or sun sensitivity; difficulty when eating dry food, the need for water at dinner

or at the bedside, sucking sweets; swollen joints or diarrhoea. The most frequent complaint was joint stiffness (50%) (Table 2). Compared to other studies[22,23,26] it can be concluded that our patients are 'low complainers'.

Antinuclear antibody positivity was found in 16% of our patients, which is less than the 20-58% prevalence of ANA reported in other studies.[22,23,26] These studies included only patients with clinial evidence of connective tissue disease. Another possible explanation for the difference in ANA positivity could be the rather short mean time from surgery until ANA testing in our study (mean 2 years; Table 1) compared to the mean time from surgery to development of symptoms of 4-10 years in other studies. It is also important to stress the prevalence of ANA in relation to the assays performed.[33] Another point to consider is the use of drugs in this patient group, such as antidepressants (chloropromazine derivatives), which are highly associated with the drug-induced lupus syndromes. The use of drugs in the past is often overlooked. A drawback is that in our study we had no data before the patients were operated on. The lack of difference in symptom expression between the ANA-positive and ANA-negative group in this study, the rather low complaint percentages (Tables 2,4) and a majority of women with a low score within the different rheumatic syndrome groups (Figs 1, 2, 3), support the non-existence of a silicone-induced disease. This is consistent with the findings of recent published studies.[13,16-18,34] These studies[16-18] investigated the prevalence of RA and CTD in cohorts of patients with SBI in order to calculate whether they were increased. All these studies are hampered by a well defined control group (how to define and match the controls with the SBI patients?), but no increased prevalences could be reported. On the other hand, in patients with a defined rheumatic disease the prevalence of SBI was not increased.

This study examined only the prevalence of rheumatic disease-related symptoms and the prevelance of ANA. We realise that our sample size of 63 women is too small to draw conclusions and make correlations, and that the overall follow-up time was rather short, but our aim was to study the prevalence of ANA and compare the symptom complex between ANA-positive and ANA-negative patients. Nothing can be said about the preexisting symptoms or change of ANA status after reconstruction. To evaluate the exact role of silicone in the induction of serological and clinical abnormalities a controlled study with ANA estimation before surgery is needed, which was started in April 1995 at the Department of Surgical Oncology at the Daniel den Hoed Center, Rotterdam. Such a study must be conducted so as to close the discussion about whether "siliconosis" is a real clinical problem and/or not an emotional issue for women with complaints after silicone implantation.

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CHAPTER II.2

A prospective study on silicone breast implants and the silicone related symptom complex

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Clinical Rheumatology 2002;21:215-219

ABSTRACT

Objective: This cohort study prospectively evaluated the prevalence of the silicone related symptom complex (SRSC) in relation to antinuclear antibodies (ANA) and magnetic resonance imaging (MRI) of the silicone breast implant (SBI) 1 year after implantation.

Methods: A total of 57 women undergoing mastectomy followed by immediate breast reconstruction (IBR) and SBI between March 1995 and March 1997 at the University Hospital Rotterdam/Daniel den Hoed Cancer Centre, were prospectively evaluated. Just before and 1 year after IBR the sera of these women were tested for the presence of ANA and they were screened for the prevalence of SRSC-related symptoms by questionnaire. All prostheses were evaluated by MRI 1 month and 1 year after IBR.

Results: Just before operation 11% of the women had a Sjögren score of more than 2, whereas 30% had such a score 1 year after IBR (P=0.01). One year postoperatively women had significantly more RA/Raynaud-related complaints: 21% preoperatively versus 40% 1 year after IBR (P=0.03). Within the undefined complaints-related group 19% had a score of 2 or more preoperatively and 33% 1 year after IBR (P=0.09). There were no new cases of ANA positivity 1 year after IBR. The linguine sign was seen by MRI in three implants: one 1 month after IBR and two 1 year after IBR. There was no relation to changes in SRSC expression and these MRI findings.

Conclusion: One year after SBI implantation women had more SRSC-related complaints, especially Sjögren's and RA/Raynaud's. Moreover there was no correlation between elevated SRSC expression and changes in the presence of ANA or changes in MRI of the SBI 1 year after IBR.

INTRODUCTION

Over recent decades the use of silicone breast implants (SBI) for both breast augmentation and reconstruction after mastectomy has increased substantially. There has been controversy in the literature about the existence of a silicone-related symptom complex (SRSC) and the results of a number of studies have associated SBI with the development of connective tissue disease.[1-6] Recently, reports have appeared about increased titres of antinuclear antibodies (ANA) in women with SBI and complaints related to SRCS.[6,7] However, results in other studies have suggested that there is little or no relationship.[8-11] We reported previously in a retrospective study that there was no difference in SRSC expression between women with SBI who were ANA positive and those who were ANA negative.[12]

Magnetic resonance imaging (MRI) of SBI has been shown to be a highly sensitive method for visualising both SBI and surrounding tissue, and is more accurate than mammography or ultrasound for detecting implant rupture.[13,14] The role of free silicone gel in relation to idiopathic or typical connective tissue disease is not clear.

The only way to answer the question as to whether SBI actually causes SRSC, is to follow patients in a prospective manner.

In 1995 the Rotterdam Working Party was founded in order to start a prospective longitudinal study to follow every woman undergoing a mastectomy followed by breast reconstruction with an SBI. In this study we evaluate the first 57 women by questionnaire dealing with SRSC, by taking sera for detection of ANA and by MRI of SBI. The aim of this study was to report the prevalence of symptoms related to SRSC, the prevalence of ANA and to discover whether a relationship can be established between SRSC, ANA and implant integrity 1 year after silicone breast implantation.

PATIENTS AND METHODS

Between March 1995 and March 1997, 57 consecutive women who underwent mastectomy followed by an immediate breast reconstruction with a subpectorally placed silicone prosthesis (Laboratoires Eurosilicone, Apt, France) at the University Hospital Rotterdam/Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands, were included in the study. The surgical oncologist performed the mastectomy in close cooperation with the plastic surgeon.

Just before IBR and 1 year after IBR the sera of these women were tested for the presence of antinuclear antibodies (ANA) using the immunofluoresence assay on HEp-2 cells at the Department of Autoimmune Disease (CLB), Amsterdam.

The women were asked to complete a questionnaire. There were specific questions related to symptoms referable to Sjögren's syndrome (keratoconjunctivitis sicca: a dry, burning, sore, red, gritty feeling and photosensitivity; and/or xerostomia: dry, difficulty when eating dry food, the

need of water at bedside/at dinner, sucking a sweet), to rheumatoid arthritis (swollen, painful and stiff joints), to Raynaud's phenomenon and to undefined complaints (headache, dizziness, palpitations, transpiration and diarrhoea). The maximal score for Sjögren-related symptoms was 12, for rheumatoid arthritis and Raynaud's phenomenon 4, and for undefined complaints 5.

All women were evaluated with MRI of the breast 1 month and 1 year after IBR. MRI was performed with a 1.5 Tesla system (Vision, Siemens, Erlangen, Germany). Before scanning, venous access was established in a cubital vein through which a bolus of contrast material, consisting of 20 ml Gadolinium-diethylenetriamine penta-acetic (Gd-DTPA) (Magnevist, Schering, Berlin, Germany) was administered during the examination. The women lay prone with the breast suspended in a double breast surface coil. After an initial localiser, a T_2-weighted sequence was performed with the following scan parameters: FOV 350 mm, contiguous slices of 5 mm thickness, scan matrix 220x256, scan time 3 min 11 s, 1 acquisition, TR/TE=9128/60 ms, TI=150 ms, flip angle 180°. Subsequently, the gradient echo T_1-weighted series were made: a two-dimensional fast low angle shot (FLASH) sequence was performed before and 1, 3 and 5 minutes after contrast administration. The 2D scan parameters were: FOV 320 mm, scan matrix 224x256, scan time 1 min, 1 acquisition, TR/TE = 290/5 ms, flip angle 90°. Subtraction images were obtained with the use of a software subtraction function. Those who read the MR images (A.I.M.O., C.M.E.C.) prospectively applied the criteria for determination of implant failure, i.e. linguine sign, noose sign, droplets or extracapsular spread of gel.[15,16] The presence of these findings and an overall impression of the implant, i.e. capsule or exudate surrounding the implant, was reported.

Statistical Analysis

The proportions of patients with complaints 1 month and 1 year after IBR were calculated for every syndrome, and they were compared using Pearson's χ^2 test or Fisher's exact test, whichever was appropriate. All P values were two-tailed and values <0.05 were considered statistically significant.

RESULTS

There were 57 women included in the study. Twenty-seven women underwent unilateral and 30 underwent bilateral mastectomies, resulting in 87 immediate breast reconstructions with silicone implants. The indications for mastectomy were prophylactic (56), breast cancer (15), extensive ductal carcinoma in situ (12) and recurrence of breast cancer after breast-conserving therapy (4). The TNM classifications of the tumours[17] are given in Table 1. The mean age at operation was 43 years (median 43, range 26–58).

Table 1. TNM classification of 27 women treated with mastectomy and IBR for breast cancer or DCIS

TNM Classification	Number
TisN0M0	12
T1N0M0	9
T1N1M0	3
T2N1M0	2
T3N1M0	1
Total	27

Table 2. Differences in rating-scale in the 57 prospectively followed patients 1 year after IBR with SBI (cumulative)

Scale	Pre-operative	Post-operative (1 year)
Sjögren:		
12	-	-
11	-	1
10	-	-
9	-	1
8	1	1
7	-	3
6	-	-
5	1	2
4	2	4
3	2	5
2	9	2
1	16	6
0	26	32
RA/Raynaud:		
4	2	5
3	6	5
2	4	13
1	24	16
0	21	18
Undefined complaints:		
5	1	1
4	1	4
3	3	5
2	6	9
1	17	8
0	29	30

ANA Positivity

Four of the 57 (7%) women were ANA positive before SBI, and one was already known to have rheumatoid arthritis. One year after SBI these women were still positive for ANA. There were no new cases of ANA positivity 1 year after SBI.

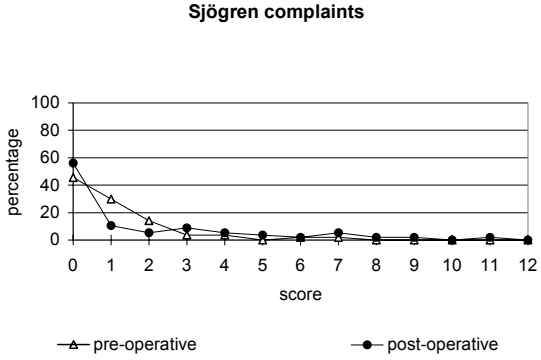

Figure 1. Sjögren complaints in 57 prospectively followed women preoperatively and 1 year after IBR with SBI

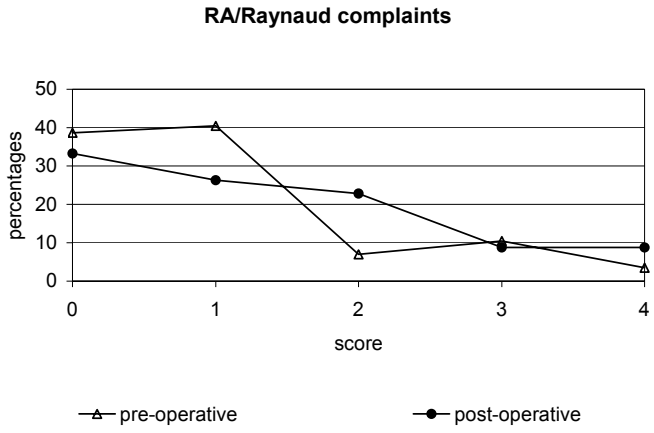

Figure 2. RA/Raynaud complaints in 57 prospectively followed women preoperatively and 1 year after IBR with SBI

Rheumatic Disease-Related Symptoms

The maximal score for Sjögren-related symptoms was 12, but none of the women had such a score, either pre- or postoperatively. Pre-operatively, 74% (42/57) of all women had a Sjögren score of 0 or 1, whereas one year postoperatively 67% (38/57) had such a score (P=0.41) (Fig. 1). Only 6 women (11%) had a score of 3 or more preoperatively, whereas postoperatively 17 women (30%) had such a score (P=0.01) (Table 2).

Seventy-nine percent (45/57) of the women had a RA/Raynaud score of 0 or 1 preoperatively, whereas 1 year postoperatively 60% (34/57) had such a score (P=0.03) (Fig. 2). Within the undefined complaints related group 81% (46/57) of the women had preoperatively and 67% (38/57) of the women had postoperatively 0 or 1 symptom (P=0.09).

Table 3. Complaints of 57 women before operation and 1 year after silicone breast reconstruction

Complaints	Answered positively (%)	
	Pre-operative	Post-operative (1 year)
Sjögren		
Eyes:		
Dry	10.5	14.0
Sore	1.8	15.8
Burning	21.1	28.1
Gritty feeling	5.3	12.3
Red	7.0	17.5
Inflammation	-	3.5
Sun sensitivity	12.3	21.1
Mouth:		
Dry	15.8	15.8
Difficulty when eating dry food	5.3	8.8
In the need for water at dinner	5.3	7.0
In the need for water at bedside	15.8	19.3
Sucking a sweet	7.0	12.3
RA/Raynaud:		
Cold fingers/toes	36.8	36.8
Joints:		
Stiffness	31.6	50.9
Painful	22.8	33.3
Swollen	10.5	14.0
Undefined complaints:		
Headache	31.6	31.6
Dizziness	10.5	21.1
Palpitations	8.8	15.8
Diarrhoea	14.0	10.5
Transpiration	17.5	29.8

In Table 3 the percentages of the presence of different symptoms are given. The only symptoms which were significantly more mentioned one year after SBI, were sore eyes (2% and 16% respectively, P=0.02), and stiffness of joints (32% and 51% respectively, P=0.04).

MRI

MRI of the 87 implants showed the linguine sign, indicating a rupture of the inner capsule, in one implant 1 month after IBR. One year after IBR two more implants had the linguine sign. None of these women had changed in ANA or Sjögren-, RA/Raynaud-, and undefined-related complaints.

One month after IBR fluid around the implant was seen in 11 cases (12%), which had disappeared 12 months after IBR.

There was a thickening of the skin in two SBI, which corresponded clinically with necrosis of the skin only once. However, in two other SBI there was necrosis of the skin, which was not confirmed by MRI. A luxation of the prosthesis was detected by MRI and confirmed clinically 1

month after IBR. No fibrous capsules developed around the implant in any of the prostheses either 1 month or 1 year after IBR.

MRI detected a contralateral breast carcinoma in two women, respectively 1 month and 1 year after mastectomy and IBR.

DISCUSSION

Silicone breast implants were introduced in 1962 and are used mainly for cosmetic augmentation and reconstruction after surgery for breast cancer.[18] Since their introduction a range of disorders has been reported, and many cases had a non-specific syndrome that did not fulfil conventional clinical and laboratory criteria for particular connective tissue disorders.[1-5] Borenstein[19] introduced the term siliconosis, a musculoskeletal pain syndrome characterised by overwhelming fatigue, fever, myalgias and arthralgias. In other studies it has been hypothesised that silicone could induce an auto-immune response. Elevated levels of anticollagen autoantibodies in women with silicone implants were reported[6,7], with the highest being found in women whose implants had ruptured or leaked.[20] Solomon et al. evaluated 176 symptomatic patients with silicone breast implants, nearly 50% of whom required explantation because of capsular contracture or rupture. The authors concluded that these observations strongly suggest that local symptomatology might identify a subgroup of women who are at a higher risk for developing systemic disease. They also suggest that local leakage of silicone incites first a local and later a systemic immune response.[5] Teuber et al.[6] reported on the relation between silicone breast implants and the risk for immunopathology based on a statistically significant incidence of antibodies to collagen in women with SBI. These women had a high incidence of capsular contracture and implant rupture.[6] Recently raised titres of ANA have been found in patients with SBI.[2,3,5] A correlation of ANA positivity with implant rupture was noted in one study.[20]

MRI is more accurate than mammography or sonography for detecting implant rupture.[13,14] In augmented breast the sensitivity ranged from 75 to 80% and from 70 to 75% for MRI and ultrasound, respectively; the specificity for implant rupture is 95% and 90%, respectively.[21-23] Furthermore, MRI is useful for evaluating capsular contracture.

The intention of the present study was to investigate prospectively the occurrence of complaints related to SRSC in relation to ANA positivity and implant integrity measured by MRI 1 year after IBR. Overall, patients had more complaints one year after SBI. In particular, the number of Sjögren and RA/Raynaud-related complaints was significantly increased. Women had also significantly more complaints of sore eyes and joint stiffness 1 year after IBR. There was no difference in ANA positivity. We take this increase in SRSC related complaints seriously. Therefore the follow-up of these women will be extended to monitor changes in SRSC complaints by questionnaire and the presence of ANA.

The linguine sign, which is suspicious of intracapsular rupture of the implant, was seen in three prostheses, but none of these women had developed SRSC-related complaints or were ANA positive 1 year after SBI.

A drawback of this study is the relative short follow-up. Studies have strongly implicated implant age as the prime factor in rupture[24-26] Disruption is directly related to time since implantation. Most implants have lost or will lose the integrity of silicone shell after between 8 and 14 years.[27] The time course of symptom evolution further suggests a direct relation to local pathology and leakage of significant quantities of silicone.[5] Our data do not allow us to distinguish between the possibility that silicone exposure will lead to the onset of connective tissue disease in women who may develop disease spontaneously at a later date, and the possibility that exposure to silicone induced de novo autoimmune-type disease. We did not find a relation between increased SRSC complaints and ANA positivity or MRI changes in the silicone prostheses 1 year after SBI. While awaiting the results of the prospective study with a third measurement of SRSC-related complaints and ANA, we accept the conclusions from large retrospective cohort studies, which could not find any risk of connective tissue disease in association with silicone prosthesis.[10,11,28-30]

CONCLUSION

Women with SBI have more Sjögren-, RA/Raynaud- and undefined-complaints 1 year after IBR. In particular, the numbers of Sjögren- and RA/Raynaud-related complaints were significantly increased. ANA serology of women 1 year after SBI did not differ from preoperatively ANA-screening. Changes in complaint-expression 1 year after SBI were not associated with MRI changes of the implants.

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CHAPTER II.3

A second prospective study on silicone breast implants (SBI) and the silicone related symptom complex (SRSC)

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Submitted for publication

ABSTRACT

Objective: This cohort study evaluates prospectively the prevalence of the silicone related symptom complex (SRSC) in relation with antinuclear antibodies (ANA) one year and at least 3 years after its implantation.

Methods: A total of 75 women, who underwent mastectomy followed by immediate breast reconstruction (IBR) with SBI between March 1995 and December 1997 at the Erasmus MC-Daniel den Hoed Cancer Centre, were prospectively evaluated. The sera of these women were tested for the presence of ANA and the prevalence of the SRSC related symptoms was screened by questionnaire, both at 3 different time-intervals: just before, one year after SBI and with a at least follow-up of 3 years after SBI.

Results: Just before operation 7% of the women had a Sjögren score of more than 2, whereas 19% had such a score one year after SBI and 9% at least 3 years after SBI (not significant (ns)). Women had postoperatively significantly more RA/Raynaud related complaints: 19% preoperatively versus 33% 1 year after SBI (P=0.04). At least 3 years after SBI 40% had RA/Raynaud related complaints (P=0.004) Within the undefined complaints related group 11% had preoperatively, 20% had one year after and 13% had at least 3 years after SBI a score of 2 or more (ns). There was one new case of ANA positivity one year after IBR. There were no new cases of ANA positivity at third ANA testing.

Conclusion: One year after SBI implantation women had more SRSC related complaints, especially Sjögren (ns) and RA/Raynaud (s) related complaints. Three years after SBI women had less Sjögren and undefined complaints, similarly to preoperative complaint scores. RA/Raynaud related complaints were significantly increased 3 years after SBI. Moreover there was no change in ANA expression one year and 3 years after SBI.

INTRODUCTION

Over the last decades, the use of silicone breast implants (SBI) for both breast augmentation and for breast reconstruction after mastectomy has increased substantially. There has been a controversy in literature about the existence of a silicone related symptom complex (SRSC). Some investigators have suggested an association between SBI and a new atypical rheumatic condition or atypical connective tissue disease.[1-7] Borenstein introduced the term siliconosis for this new symptom complex, a musculoskeletal pain syndrome characterised by overwhelming fatigue, fever, myalgias and arthralgias.[6] Moreover, reports have appeared about increased titres of antinuclear antibodies (ANA) in women with SBI and complaints related to SRCS.[7,8] However results in other studies have suggested that there is little or no relationship.[9-12] We reported previously in a retrospective study that there was no difference in SRSC expression between women with SBI who were ANA positive or ANA negative.[13]

The only way to get an answer to the question if SBI actually causes SRSC, is to follow patients in a prospective manner. Therefore, in 1995 the Rotterdam Working Party was founded in order to start a prospective longitudinal study to follow every woman undergoing a mastectomy followed by breast reconstruction with an SBI. Recently a first analysis of these data has been published[14], in which it is concluded that patients had more complaints after SBI. Especially the scores of Sjögren and RA/Raynaud related complaints were significantly increased. Women had also significantly more complaints of sore eyes and stiffness of joints one year after IBR. There was no difference in ANA positivity. Due to this increase in SRSC related complaints, the follow-up of these women is extended to a minimum of 3 years. In the present study an evaluation is made of the first 75 women by questionnaire dealing with SRSC and by taking sera for detection of ANA before, one year and at least 3 years after SBI. The aim of this study is to report the prevalence of symptoms related to SRSC, the prevalence of ANA and to study if a relationship can be established between SRSC and ANA.

PATIENTS AND METHODS

Between March 1995 and June 1997, 93 consecutive women who underwent a mastectomy followed by an immediate breast reconstruction with a subpectorally placed silicone prosthesis (Laboratoires Eurosilicone, Apt, France) at the Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands, were included in this study. The surgical oncologist performed the mastectomy in close co-operation with the plastic surgeon, who reconstructed the breast with a subpectorally placed silicone prosthesis. The surgical details have been described elsewhere.[15]

Just before SBI (ANA I), one year after (ANA II) and at least 3 years after (ANA III) SBI the sera of these women have been tested for the presence of antinuclear antibodies (ANA) and by questionnaire for Sjögren-, RA/Raynaud-, and undefined complaints. ANA testing was done by

using the immunofluoresence assay on HEp-2 cells at the Department of Autoimmune Disease (CLB), Amsterdam. There were specific questions related to symptoms referable to Sjögren's syndrome (keratoconjunctivitis sicca: dry, burning, sore, red, gritty feeling and photo-sensibility and/or xerostomia: dry, difficulty when eating dry food, the need of water at bedside/at dinner, sucking a sweet), to rheumatoid arthritis (RA) (swollen, painful and stiff joints), to Raynaud's phenomenon and to undefined complaints (headache, dizziness, palpitations, transpiration and diarrhoea). The maximal score for Sjögren related symptoms was 12, for RA/Raynaud's phenomenon 4, and for undefined complaints 5.

Statistical Analysis

The proportions of patients with complaints before, one year after and at least 3 years after SBI were calculated for every syndrome, and for every two time points they were compared using Pearson's chi-squared test or Fisher's exact test, whichever was appropriate. All P-values were two-sided and P-values ≤ 0.05 were considered statistically significant.

RESULTS

Between March 1995 and Decembre 1997, 93 women had been operated. At ANA III testing 7 women were dead, 4 had active metastatic disease, 6 were lost for follow-up and 1 had lost her prosthesis, resulting in 75 women in whom a third ANA testing and questionnaire was completed. These women were included in this study. The mean age at SBI was 43 years (median 44; range 27-59 years). Twenty-four women underwent unilateral and 51 women underwent bilateral mastectomies followed by IBR with silicone implants. The indications for mastectomy were prophylactic (36), breast cancer (26), extensive ductal carcinoma in situ (13).

ANA-testing

The mean age at ANA I testing was 43 years (median 44; range 26-59 years), at ANA II testing 45 years (median 45; range 28-60 years) and at ANA III testing 48 years (median 48; range 30–64 years). Two of the 75 (2.7%) women were ANA positive before SBI (ANA I). One of these women was already known with rheumatoid arthritis. One year after SBI (ANA II) these women were still positive for ANA and there was one new cases of ANA positivity (1%) one year after SBI. The women who was negatively ANA tested before and positively ANA tested one year after SBI, was ANA negative 5.3 years after SBI. There were no new cases of ANA positivity at third ANA testing (ANA III).

Rheumatic Disease Related Symptoms

The maximum score for Sjögren related symptoms was 12, but none of the women, pre- or post-operatively, had such a score. Pre-operatively 81% (61/75) of all women had a Sjögren score of

Table 1. Differences in rating-scale in the 75 patients one year and at least 3 years after IBR with SBI (cumulative)

Scale	Pre-operative	Post-operative (1 year)	Post-operative (min 3 years)
Sjögren:			
12	-	-	-
11	-	1	-
10	-	-	-
9	-	-	-
8	-	-	-
7	-	2	-
6	-	-	-
5	1	2	1
4	2	4	2
3	2	5	4
2	9	4	2
1	13	7	7
0	48	50	59
RA/Raynaud:			
4	2	5	3
3	7	7	14
2	5	13	13
1	31	19	24
0	30	31	21
Undefined complaints:			
5	-	-	1
4	1	3	-
3	3	4	4
2	4	8	5
1	15	15	12
0	52	45	53

0 or 1, whereas one year postoperatively 76% (57/75) and at least 3 years postoperatively 88% (66/75) had such a score (Fig 1). Only 5 women (7%) had pre-operatively a score of 3 or more, whereas one year postoperatively 14 women (19%) (P=0.03) and at least 3 years postoperatively 7 (9%) had such a score (not significant (ns)) (Table 1). Eighty-one percent (61/75) of the women had a RA/Raynaud score of 0 or 1 preoperatively, whereas one year postoperatively 67% (50/75) (P=0.04) and at least 3 years postoperatively 60% (45/75) (P=0.004) had such a score (Fig 2/Table 3). Within the undefined complaints related group 89% (67/75) of the women had preoperatively, 80% (60/75) of the women had 1 year postoperatively, and 87% (67/75) of the women had at least 3 years postoperative 0 or 1 symptom (ns) (Table 1).

In Table 2 the percentages of the presence of different symptoms are given. The only symptoms which were significantly more mentioned one year and at least 3 years after SBI, were stiffness of joints (24%, 45% and 45% respectively, P=0.006) and painful joints (pre-operatively 17%, at least 3 years postoperatively 40%, P=0.002). Burning eyes and sucking a sweet were significantly less mentioned at least 3 years after SBI (P=0.008 and P=0.03 respectively).

Table 2. Complaints of 75 patients before operation, 1 year after, and at least 3 years after silicone breast reconstruction

Complaints	Answered positively (%)		
	Pre-operative	Post-operative (1 year)	Post-operative (3 year)
Sjögren			
Eyes:			
Dry	4.0	8.0	2.7
Sore	-	8.0	1.3
Burning	12.0	18.7	4.0
Gritty feeling	2.7	5.3	5.3
Red	1.3	8.0	1.3
Inflammation	-	-	1.3
Sun sensitivity	10.7	16.0	8.0
Mouth:			
Dry	13.3	12.0	8.0
Difficulty when eating dry food	4.0	5.3	5.3
In the need for water at dinner	2.7	4.0	6.7
In the need for water at bedside	10.7	12.0	2.7
Sucking a sweet	5.3	10.7	1.3
RA/Raynaud:			
Cold fingers/toes	45.3	34.7	38.7
Joints:			
Stiffness	24.0	45.3	45.3
Painful	17.3	25.3	40.0
Swollen	6.7	9.3	14.7
Undefined complaints:			
Headache	16.0	22.7	14.7
Dizziness	6.7	12.0	8.0
Palpitations	5.3	9.3	8.0
Diarrhoea	8.0	6.7	5.3
Transpiration	12.0	22.7	16.0

Table 3. SRSC-related complaints, preoperative, 1 year postoperative, and at least 3 years postoperative

time-interval	complaints		
	Sjögren ≥ 2	RA/Raynaud ≥ 2	undefined ≥ 2
pre-SBI	18%	19%	11%
one year after SBI	24%	33%*	20%
At least 3 years after SBI	12%	40%**	13%

* P=0.04
** P=0.004

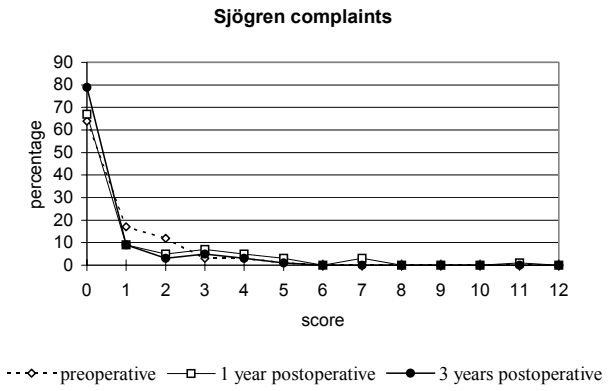

Figure 1. Sjögren complaints in 75 patients preoperatively, 1 year and at least 3 years after IBR with SBI

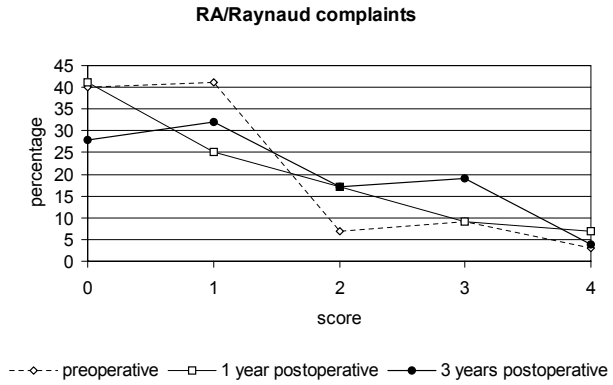

Figure 2. RA/Raynaud complaints in 75 patients preoperatively, 1 year and at least 3 years after IBR with SBI

DISCUSSION

Silicone breast implants have been introduced in 1962 and are mainly used for cosmetic augmentation and reconstruction after surgery for breast cancer.[16] Since its introduction a range of disorders has been reported, and many cases had a non-specific syndrome that did not fulfil conventional clinical and laboratory criteria for particular connective tissue disorders.[1-6] Solomon et al evaluated 176 symptomatic (chronic fatigue, cognitive dysfunction, sicca syndrome, arthralgia) patients with silicone breast implants.[5] Nearly 50% of these patients required explanation due to capsular contracture or rupture. Forty percent of those patients who had permanent explanation surgery considered themselves to have significant improvement in their symptoms. They concluded that these observations strongly suggest

that local symptomatology might identify a subgroup of women who are at a higher risk for developing systemic disease. Recently Brown et al confirmed this suggestion.[17] In their study extracapsular silicone was associated with an increase in self-reported physician-diagnosed fibromyalgia and other connective tissue disease in women with SBI.[17]

In other studies it has been hypothesised that silicone could induce an auto-immune response. Elevated levels of anti-collagen auto-antibodies in women with silicone implants were reported[7,8,18], with the highest antibody levels being found in women whose implants had ruptured or leaked.[18] It has also been suggested that local leakage of silicone incitied first a local and later a systemic immune response.[5] Teuber et al.[7] reported on the relation between silicone breast implants and the risk for immunopathology based on a statistically significant incidence of antibodies to collagen in women with SBI. These women had a high incidence of capsular contracture and implant rupture.[7]

However, when a connective tissue disease (CTD) is suspected, the simplest screening test and practical starting point is testing for ANA. A positive ANA test gives support to the diagnosis of CTD. On the other hand, in some patients, the cause of a positive ANA is never satisfactorily explained and the presence of ANAs in healthy people has been documented. General, the frequency of ANA increases with age: 6% of women in the fertile population[19] and 15-30% of women over the age of 60[20] are ANA positive. Recently raised titres of ANA have been found in patients with SBI.[2,3,5,18,21] A correlation of ANA positivity with implant rupture was noted in one study.[18]

Recently we published data on which it was concluded that patients had more complaints one year after SBI.[14] Especially the scores of Sjögren and RA/Raynaud-related complaints were significantly increased. Women also had significantly more complaints of sore eyes and stiffness of joints one year after IBR. There was no difference in ANA positivity. Moreover there was no correlation between elevated SRSC expression and changes in the presence of ANA or changes in MR imaging of the SBI one year after IBR. Due to this increase in SRSC related complaints, the follow-up of these women was extended with a minimum of 3 years. In the present study patients had less Sjögren and undefined complaints at least 3 years after SBI (comparable to preoperative percentages), whereas RA/Raynaud complaints were significantly increased one and 3 years after SBI. Once more there was no difference in ANA expression 3 years after SBI. Therefore, this increase in complaints could probably not be explained on an immunological basis. A flaw of this study is the lack of an age-controlled group. In literature several studie mentioned the prevalence of musculoskeletal pain (mean 25%) in the general population, which systematically increases with age[22,23,24], with a positive trend between menopause and joint pain.[25,26]

Moreover, several large retrospective cohort studies could not demonstrate a potential association between SBI and CTD.[11,12,27-29] Recently, two meta-analyses have evaluated the available data on silicone breast implants.[30,31] Both concluded that an association between SBI and CTDs has not been demonstrated and is unlikely to exist.

Although women have an increase of RA/Raynaud-related complaints one and at least 3 years after SBI, evidence for an immunological cause was not found. However, women should preoperatively be informed about these increased symptoms.

CONCLUSION

Women with SBI do not have more Sjögren-, and undefined- complaints one and at least 3 years after IBR. There is a significant increase in RA/Raynaud complaints one and 3 years after SBI; especially stiffness of joints and painful joints are significantly increased. ANA serology of women one year and 3 years after SBI did not differ from preoperatively ANA-screening.

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CHAPTER III.1

Motivations, satisfaction, and information of immediate breast reconstruction following mastectomy

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Patient Education and Counseling 2000;40:201-208

ABSTRACT

Objective: This study evaluated patients' motivation for, and satisfaction with the treatment and information of immediate breast reconstruction (IBR) with a silicone prosthesis. It studied satisfaction more deeply by relating it to the quality of life, body-image and sexual functioning.

Methods: Seventy-three patients who received mastectomy, followed by IBR with a subpectoral silicone prosthesis, completed a self-report questionnair concerning their motivations for, perceived adventages of, and satisfaction with IBR, the information received, quality of life, body image, and sexual functioning.

Results: Despite the fact that 50% of the reconstructions resulted in complications or complaints, 70% of the women were satisfied with the reconstruction and only 12% would never choose IBR again. Satisfaction was strongly correlated with the need for information. The higher patients' expectation, the higher their need for information. The most common perceived adventage of IBR was the avoidance of an external prosthesis.

Conclusions: A majority of patients were satisfied with the breast reconstruction. However, a sizeble portion of these women needed more information about breast reconstruction and the use of silicone prosthesis. To avoid too high expectations more attention should be given to possible complications and the moderate cosmetic results.

INTRODUCTION

In recent years, the surgical treatment of breast cancer has made significant advances: from Halsted's 'radical' mastectomy, in which both pectoral muscles are removed en bloc with the breast and axillary lymph nodes; to the Patey or Madden modified radical mastectomy; to breast conserving therapy (BCT), which combines lumpectomy and axillary lymph node dissection, followed by radiation of the breast. Studies comparing the psychological impact of mastectomy and BCT show advantages for BCT on body-image[1-7] and sexual satisfaction.[3,5,6,8,9] However, other psychological advantages, such as fewer feelings of depression or loneliness, or a better quality of life, have not been consistently reported in these studies.

BCT is not recommended for all patients. Depending on the size, location or pathological features of the tumour, mastectomy may be preferable. In these cases, breast reconstruction may be the means to improve cosmesis. Studies looking at mastectomy with and without breast reconstruction show the same psychological advantages when comparing mastectomy and BCT: greater satisfaction with the body-image[10-14] and with sexual functioning.[15] The most common reasons given by women for their choice of breast reconstruction are a reluctance to have an external prosthesis, the chance to wear a greater variety of clothing and a desire to restore their feelings of wholeness and body-integrity.[10,13,14,16-19]

There are various methods of breast reconstruction, the choice of which is dependent on the preference of the surgeon, in consultation with the patient. The women studied by Stevens et al.[14] and Schain et al.[13] showed more psychological benefit from immediate breast reconstruction (IBR) than from a delayed operation: this includes less depression, less time to mourn the complete loss of a breast, and not having to endure mutilation while waiting for reconstruction. An additional advantage is that immediate breast reconstruction alleviates the need for a second operation. Later reconstruction is more difficult because of skin restriction.

For the reconstruction of the breast, surgeons can use patients' own body tissue, such as the latissimus dorsi myocutaneous flap or the transverse rectus abdominous myocutaneous (TRAM) flap. Such procedures involve major operations, with additional scars on the back or abdomen and morbidity; for instance weakness of the abdominal wall after TRAM flap. Silicone or saline-filled breast implants do not have these disadvantages. The prosthesis can be implanted through one incision in a relative simple operation. Silicone implants have the advantage over saline filled implants of being less permeable and thereby having a higher chance of remaining the same volume. Furthermore, silicone implants are better at mimicing natural breast movements.

Because of these advantages, the Department of Surgical Oncology of the Dr. Daniel den Hoed Cancer Center in 1990 adopted IBR with the use of a subpectoral placed silicone-gel prosthesis as its preferred procedure. Subsequently, however, silicone implants became a topic of concern in the medical literature, as well as in the media, reporting both systemic and local

complications.[18,20-22] Since 1994 several cohort studies have described the introduction of an atypical connective tissue disease or of rheumatic complaints with silicone breast prosthesis.[23-26]

Winer et al.[22] concluded that a significant proportion of patients are worried about possible medical complications as a consequence of silicone breast implants. As implications of their research they stated: "the true risks associated with silicone implants will ultimately be known. In the mean-time, health care providers need to address patients' concerns about these implants. Information and guidance regarding the potential benefits and risks of breast implant devices should be provided to women with breast cancer who are considering treatment options."

Because of these concerns and controversy, we decided to carry out our own study of patients's motivation and satisfaction with silicone-implant IBR; and, more particularly, with the psychological aspects related to it.

In this study, we were interested in patients' motivation for, and satisfaction with IBR. Furthermore, we wanted to look at satisfaction in more detail, since quality of life, body-image and sexual functioning were mentioned in the literature as variables of importance.

For motivation, we looked at the reasons patients mentioned for their choice of IBR, as well as their construed advantages of IBR. Satisfaction was looked at from two points of view: the treatment as such, and the information provided for the treatment. As far as satisfaction with the treatment was concerned, satisfaction was operationalised in terms of questions such as: would the patients recommend IBR to other patients? Would they recommend IBR with silicone prosthesis to other patients? Would they choose the same treatment again? Were they satisfied with the reconstruction? And, did they have complaints about the reconstruction? Satisfaction with the received information looked at items measuring the need for more information about: the use of silicone prosthesis; the advantages and disadvantages of IBR; the results of breast reconstruction; and, how to cope with specific problems and where to find help. In order to find out how important the information was for the satisfaction of the treatment, the relation between the two were studied. Quality of life, body image and sexual functioning were also looked at in relation to satisfaction.

PATIENTS AND METHODS

Sample

Between September 1990 and May 1995, at the Academic Hospital Rotterdam/Dr. Daniel den Hoed Cancer Centre, 103 women were treated by mastectomy followed by IBR with a subpectorally implanted silicone prosthesis. The operations were performed by a general surgeon and a plastic surgeon.

Development and Provision of Information

Information-modules were developed by a working group consisting of two surgeons, a plastic surgeon, a rheumatologist, a radiologist and a health psychologist. These modules contained (1) information about the surgical procedure and its possible complications (2) the different methods and surgical techniques of breast reconstruction (3) an account of IBR with the use of silicone prosthesis (4) the advantages of the use of silicone prosthesis and a summary of the controversy over the use of the silicone implants and (5) an explanation of the importance of attending check-ups and reporting complaints. Photographic illustrations were provided of various cosmetic results of IBR.

During a consultating with their surgeon, the aim and instruments (modules, questionnaire) of the study and were explained to patients and they were asked for their informed consent. If they agreed to participate in the study, they received the information modules. Within 2 weeks, a further consultation with the plastic surgeon followed for all patients (whether or not patients showed their willingness to participate in the study), at which the recommended surgical treatment was discussed.

Questionnaire

All women, except one who died, received a self-report questionnaire after an interval of at least one year following the operation. The questionnaire was divided in 5 sections dealing with: (i) demographic details; (ii) motivation and perceived advantages of IBR; (iii) satisfaction with IBR; (iv) information; (v) quality of life, body image and sexual functioning.

Some items replicated questions used in previous research[27] or were part of excisting scales (Quality of Life: Rotterdam Symptom Checklist, RSCL).[28] The other items were designed by the researchers of this study.

Analyses

Data were analyzed using SPSSX (statistical package of the social sciences). Analyses used were: frequency analysis, Pearson's product-moment correlation, and factor and reliability analysis for scale construction.

Scale Construction

All variables of interest for this study were based on the formation of the various item into scales. The criteria for the scale construction, based on methodological conventions and considerations of the results of the factor- and reliability analysis, were: eigenvalue>1.0, factor loading>0.40, maximum variance accounted for, and Cronbach's α>0.60.

In Table 1, the results of the scale construction are presented. The satisfaction score is based on the total score of the seven items reflected in Table 4. The reliability of the scale is α: 0.86 and 56% of the variance is explained by these items. Information was based on the answers of the five questions as presented in Table 5. Cronbach's α was 0.76 and 53% of the variance was

explained by these questions. Quality of life was divided in physical and psychological quality of life and was measured with the physical and psychological complaints of the Rotterdam Symptom Checklist (RSCL).[28] Both contained 12 items and had α values of, respectively, 0.85 and 0.94. Psychological quality of life explained 61% of the variance; physical quality of life 43%. Body image was measured with items used by Bergman and van Dam.[27] Three example items of the six items are: as far as my breasts are concerned I (1) feel no shame walking around naked (2) find it diffecult to look at myself when getting changed (3) find it diffivult to touch my reconstructed breast. Answer categories were 'very true', 'true', 'not at all true'. This scale had an α value of 0.79, and the items explained 50% of the variance. Sexual functioning was made up of five items specially constructed for this study. Three example items are: (1) through IBR I think I remained sexual attractive (2) through IBR my sexual life can continue undisturbed (3) through IBR there is no need for my partner to feel inhibited in our sexual relation. The answer categories were the same as for the body image items. This scale had an α value of 0.89 and explained 70% of the variance.

RESULTS

Patients

Of the 102 patients, 73 completed and returned the questionnaire. Their age ranged from 26 to 64 years (mean 41.5 years). Sixty-two women had received unilateral and eleven bilateral resulting in 84 immediate reconstructions with a subpectoral placed silicone implant. The indications for mastectomy were breast cancer in 57, extensive carcinoma in situ in 18 and prophylactic mastectomy in 9.

Motivation

In Table 2, patients' motivations to receive IBR are presented. Patients answered questions about motivations with 'agree' or 'disagree'. Almost all patients stated that their motivation for IBR was to endure the amputation more easily (97%) and not to have an external prosthesis (93%). For

Table 1. Details of the different scales: number of items, Cronbach's α, explained variance and eigenvalue

Scale	Cases (n)	Items (n)	Cronbach's α	Explained variance (%)	Eigenvalue
Satisfaction	47	7	.86	56	3.94
Information	54	5	.76	53	2.64
Quality of life physical	62	12	.85	43	5.19
Quality of life psychological	60	12	.94	61	7.32
Sexual functioning	47	5	.89	70	3.50
Body image	60	6	.79	50	2.97

Table 2. Motivations for immediate breast reconstruction

Motivations	Agree (%)
To endure the amputation more easily	97
Not to have an external prosthesis	93
Not to be mutilated by the mastectomy	89
To feel feminine again	80
To remain sexually attractive	75
To avoid changes in sexual relation	67

Table 3. Advantages of immediate breast reconstruction

Advantages	Agree (%)
Not to have an external prosthesis	87
To feel feminine again	70
To avoid changes in sexual relation	70
To have an unchanged sexual relation with the partner	69
To have the feeling of having something of one's own again	69
To have more confidence	66
To wear a bra when desirable	63
To stay sexually attractive	61
To feel oneself again	57
To get rid of the cancer	50
To endure the amputation more easily	44

Table 4. Items of the satisfaction scale

Item	Yes (%)
Would recommend IBR to other patients	95
Would recommend IBR with silicone prosthesis to other patients	80
Would dissuade other patients with silicone prosthesis from having IBR	20
Would do it again	76
Satisfied with reconstruction	70
Breast reconstruction meets expectation	62
Complaints about reconstruction	58

more than threequarters of the patients, IBR was also important as way of avoiding mutilation (89%) and to feel feminine again (80%). Seventy-five percent of the patients were motivated to receive IBR because they wanted to remain sexually attractive and 67% because they wanted to avoid changes in their sexual relations.

Advantages

The most important perceived advantage of IBR was not to have to wear an external prosthesis (87%) (Table 3). Other advantages concerned feelings of feminity (70%) and sexuality (70%). It is interesting to note that for a few patients their sexual relation is construed differently from sexual attractiveness in relation to IBR. Another interesting finding was that although the endurance of the amputation was seen by almost all patients as a motivation for IBR, this was not seen by so many patients as an advantage of IBR.

Satisfaction with the Treatment

Patients' satisfaction with IBR by silicone prosthesis was measured in terms of seven questions (Table 4). Almost all patients would recommend IBR to other patients (95%). Only nine women would never choose immediate breast reconstruction again, would not recommend it to other patients and would even try to dissuade them from having the treatment. They were concerned about the possible complications associated with silicone gel implants (three patients); had had a disappointing cosmetic effect (three patients), postoperative complications (two patients) or an unspecified preference for a water-filled prosthesis (one patient). More than two-third were satisfied with the reconstruction and would undertake it again. More than half of the patients had complaints about the prosthesis.

Satisfaction with the Information

Even though the oral information was supplemented by providing the patients with written information which they could take home, they still had a need for more information (Table 5). They would have especially liked more information about the use of silicone prosthesis (57%), the advantages and disadvantages of immediate reconstruction (55%) and the results of the breast reconstruction (52%). In general, more patients (80%) were satisfied with the information which they had about how to cope with specific problems and where to find help.

Relation between Satisfaction with IBR and Need for Information

The correlations between the satisfaction factor and three information items, information about the results of IBR, the dis/advantages of IBR and the use of silicone prosthesis, respectively, are significant. For all three of these items, the correlation is negative, meaning, the less satisfied patients were with IBR, the higher was their need for more information about the results ($r=-0.58$) and advantages and disadvantages ($r=-0.51$) of IBR and the use of a silicone prosthesis ($r=-0.48$). In relation to this finding we looked at the expectation item of the satisfaction scale

Table 5. Items of the information scale

Need for more information about:	Yes (%)
The use of silicone prosthesis	57
Dis/advantages of immediate reconstruction	55
Results of breast reconstruction	52
Breast cancer and its treatment	40
Coping with specific problems and knowing where to find help	20

Table 6. Correlation between satisfaction and other scales

Scale	satisfaction	
	r	P <
Quality of life psychological	-0.64	0.001
Quality of life physical	-0.37	0.01
Body image	0.50	0.001
Sexual functioning	0.16	ns

in more detail: what was the correlation between the degree of agreement with the statement that the breast reconstruction met the patient expectation and the three significant information items with satisfaction. We found, that the higher patients' expectations were, the higher was their need for information about the results of breast reconstruction (r=0.52), the advantages and disadvantages of IBR (r=0.42) and the use of silicone prosthesis (r=0.42).

Relation between Satisfaction with IBR and Quality of Life, Body Image, and Sexual Functioning

In Table 6, the correlation between satisfaction with IBR and psychological and physical quality of life, body image, and sexual functioning are given. All, but sexuality, correlate significantly with satisfaction. The highest correlation is with psychological complaints (r=-0.64). The more satisfied the patient is with IBR, the fewer psychological complaints she had and vice versa. For physical complaints, this correlation was lower (r=-0.37). The correlation of satisfaction and body image was r=0.50: the more a patient accepted her body, the more satisfied she was.

DISCUSSION

Although our patients received IBR and did not have the experience of an external prosthesis, one of their most common motivations for reconstruction was "not to have an external prosthesis". This is similar to the findings of other studies.[13,16,29] However, there is a slight difference in the percentages between the item "not to have an external prosthesis" as a motivation or advantage. A possible explanation for this could be the lack of experience with

the external prosthesis of patients in this study in comparison with the patients in studies which looked at the effects of delayed reconstruction.

The other findings from the present study concerning motivations and advantages are similar to those in the study of Bergmann and Van Dam.[27] However, contrary to the outcome of that study, the motivations leading to reconstruction and advantages perceived by patients are not in the same order, especially the item 'to endure the amputation better' (resp. 97% (first mentioned) versus 44% (last mentioned)). This may be explained by the relatively high complication rates caused by the prosthesis (58%), which might have reminded women of their amputation. In general, the percentages of advantage-items are lower than those of the corresponding motivation-items (Table 2, Table 3, respectively), which can probably be explained by 38% of the women who had higher expectations of IBR. Comparing motivation and advantages, one of the criticism of this study one could think of is that correlation only can be obtained by prospective study.

On the whole, patients were satisfied with their breast reconstruction by silicone implants. The controversy about the use of silicone did not seem to affect many of them. Only three women indicated that, because of the possible complications associated with silicone prosthesis: they (i) would never choose a silicone prosthesis again (ii) would not recommend it and (iii) would even try to dissuade others from choosing the procedure. Merkatz et al.[21] found a relation between the disappointing experiences with silicone implants expressed by women and a lack of information, inadequate follow-up and not being taken seriously when reporting complaints. The disappointing experiences with silicone implants which were expressed by patients in the present study were also related to a lack of information: 57% of women were in need of more information about the use of a silicone prosthesis (Table 5). This need was strongly correlated with satisfaction rate (Table 6).

Even though patients received both oral and written information the latter specially developed for this study more than half of the patients were also in need of other information. This is in the line with several other studies[e.g. 30,31], however, questions remain as regards information presentation. What more information should be presented in order for patients to be satisfied? Should patient information be uniform, or should there be a mode of presentation, such as multimedia, which enables patients, at an individual level, to look for the information they need. Is it the information as such which is important, or is it a matter of high expectations of the outcome of the reconstruction? Significant high correlations between disappointed expectations and the expressed need for more information seem to support this last suggestion.

In spite of the findings of Bergman and Van Dam[27], data in this study show that sexuality does play a role in the choice of breast reconstruction. This is also confirmed by other studies.[12,15,29] Even though sexuality was a frequently mentioned motivation and focus of perceived advantage, it did not seem to be important for satisfaction with the breast reconstruction itself: women might be dissatisfied with the results of the reconstruction, but this does not mean

to say that their sexual relation is unsatisfied. Reaby and Hort[29] found that a mediating factor, when deciding whether or not to have postmastectomy breast reconstruction, might be the feeling of some women that breasts were an important factor in attracting a mate. However, they concluded that both groups, reconstructed and non-reconstructed, admitted that sexuality involved more than having breasts and that concealing or covering the mastectomy area did not enhance their sexuality.

CONCLUSION

More than the half of the patients have complaints about the prosthesis. Nevertheless, 70% of them were satisfied with the reconstruction. The satisfaction rate was stongly and inversely correlated with the need for information. From this study it was not clear whether information was used as a consonant to balance the cognitive dissonance of this complaint versus satisfaction process. More research is needed to get a deeper insight into these cognitive psychological processes. However, an exchange of one's personal experience of IBR with partners in distress can be an useful addition to information provision. Accurate information about expected outcome of the operation and about possible complications are essential to avoid disappointments. The authors of this article suggest that women who are to undergo mastectomy should be informed about the possibility, and the advantages and disadvantages of the different methods of breast reconstruction. From this study, we believe that immediate reconstruction of the breast with silicone implants deserves a place among the treatments for breast cancer. It is the patient who decides whether or not she wants a breast reconstruction; and the plastic surgeon decides whether such a request can be granted, in consultation with the surgeon. We would stress that patients need accurate information prior to operation about the procedure and the use of a silicone prosthesis and require intensive follow-up, but more research is needed into the effectiveness of the design and content of this information.

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CHAPTER III.2

Satisfaction and prosthesis related complaints in women with immediate breast reconstruction following prophylactic and oncological mastectomy

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Submitted for publication

ABSTRACT

Objective: This study evaluated patients' satisfaction with immediate breast reconstruction (IBR) with silicone prosthesis. Special attention is paid to the differences in satisfaction, and specific prosthesis related complaints of IBR after prophylactic and oncological mastectomy.

Methods: All women who were operated between April 1995 and May 1999 at the University Hospital Rotterdam/ Dr Daniel den Hoed Cancer Centre received one year following operation a self-report questionnaire, concerning their perceived advantages of and satisfaction with IBR, their prosthesis-related complaints and various psycho-social variables.

Results: The most important perceived advantage of IBR was not to have to wear an external prosthesis (95%). Despite the fact that one third of the patients had related complaints about the reconstruction, 80% was satisfied with IBR and 88% would do it again. There was no significant difference in satisfaction between the prophylactic and the cancer group. Overall satisfaction was mostly influenced by cosmetics (r=-.58), information (r=-.45) and specific prosthesis related complaints (r=-.39). Especially specific prosthesis related complaints were important for both the prophylactic and the cancer group.

Conclusions: The majority of patients are satisfied with IBR after oncological or prophylactic mastectomy. However the findings of the importance of specific prosthesis related complaints should be taken serious for the information and care of patients.

INTRODUCTION

The surgical treatment of breast cancer has made significant advances. At the end of the nineteenth century Halsted introduced the radical mastectomy in which both pectoral muscles en bloc with the breast and ipsilateral axillary lymph nodes are removed.[1] The modified radical mastectomy was developed by Patey in 1932 in which the breast, including the pectoral fascia, is dissected of the pectoral muscle.[2] Nowadays breast-conserving therapy (BCT), which combines lumpectomy and axillary lymph node dissection, followed by radiation of the breast is widely embraced as an acceptable standard of care in the management of breast cancer.[2,3] BCT is not recommended for all patients. Depending on size or pathological features of the tumour, mastectomy may be preferable. In these cases, breast reconstruction may be the means to improve cosmesis. Several studies compared quality of life for patients with breast cancer who underwent mastectomy alone and mastectomy with breast reconstruction. The majority of these studies showed psychological advantages: higher satisfaction with both body image[5,6], and sexual functioning.[7]

Treatment options for women with a genetic predisposition to develop breast cancer are regular surveillance, chemoprevention, or prophylactic bilateral mastectomy. If a woman chooses for prophylactic surgery, a breast reconstruction may be considered. Prophylactic mastectomy in women at increased risk for breast cancer remains a controversial procedure.[8,9] Two studies used statistical models to predict the benefit of prophylactic mastectomy in high-risk women[10] or in mutation carriers.[11] They modelled a 90% and an 85% reduction in risk of breast cancers respectively. Although these results are very optimistic about the prophylactic mastectomy, caution should be used with the interpretation, while waiting for prospective studies focusing on the different treatment strategies in high-risk women. Meijers-Heijboer et al.[12] recently published a prospective study on 139 women with a proven BRCA1 or BRCA2 mutation. Half of the women underwent PM and the others chose for regular surveillance. After a median follow-up of 2.2 years, no breast cancer was observed after PM, while under regular surveillance 8 incident breast cancers were diagnosed. Although in this latter study the follow-up is short and the number of patients is limited, it is concluded that PM in proven mutation carriers strongly reduces the incidence of breast cancer.

One study has shown that women at high risk of breast cancer who are undergoing prophylactic surgery were satisfied with their decision, although comfort with reconstruction was mixed.[13] Another study reported that 5% had later regrets about the surgery.[14] The psychological and sexual problems in women with prophylactic mastectomy may approximate those seen in women with oncological mastectomy.[15,16] However, the psychological effects of bilateral mastectomy have not been determined for large groups of asymptomatic women undergoing this procedure to prevent breast cancer. This issue is beyond the purpose of this study in which we partly focus on IBR after prophylactic mastectomy. In the Daniel den Hoed

Cancer Centre 84% of the women with a prophylactic mastectomy chooses for immediate breast reconstruction.[17]

Historically, almost all breast reconstructions were delayed for months or years after mastectomy. It was feared that immediate breast reconstruction (IBR) would compromise adjuvant treatment, increase the risk of postoperative complications, or mask locoregional recurrence. Due to the evolution of reconstructive techniques and the increased availability of the plastic surgical expertise, IBR after mastectomy has become a good alternative for delayed reconstruction. IBR alleviates the need for a second operation and shows more psychological benefit compared to delayed reconstruction. This includes less depression, less time to mourn the complete loss of the breast, and not having to endure mutilation while waiting for a second operation.[5,6] Other studies show a decrease in anxiety and depression[18] and a significant better body image, self-esteem and sexual feeling of attractiveness and satisfaction when comparing immediate breast reconstruction over delayed reconstruction.[18,19]

The different methods for breast reconstruction compromise the use of prosthetic material, or autogenous tissue, or a combination of the two. In general the aesthetic results from autogenous tissue reconstruction are superior to those of prosthetic reconstruction.[20,21] On the other hand the prosthetic reconstruction is the simplest method with the shortest operating time. Furthermore the insertion of an implant subpectorally theoretically minimises the risk of masking recurrent disease.

In 1990 immediate breast reconstruction (IBR) with a subpectorally placed silicone prosthesis after mastectomy, on prophylactic or oncological indication, has been introduced in the Daniel den Hoed Cancer Centre. From 1995 a study started to research the effects of this treatment with the aim to evaluate the satisfaction with IBR. Furthermore, satisfaction would be studied in more detail since quality of life, body image, and sexual functioning were discussed in the literature as variables of importance. Special attention is paid to the differences in satisfaction, and specific prosthesis related complaints of IBR between the different operation indications, i.e. after prophylactic or oncological mastectomy.

PATIENTS AND METHODS

Sample

Between April 1995 and May 1999, at the University Hospital Rotterdam/Daniel den Hoed Cancer Centre, 139 women were treated with mastectomy followed by IBR with a subpectorally placed silicone prosthesis. Sixty-eight patients were treated for breast cancer and 71 patients had a prophylactic mastectomy. The operations were performed by one of the two surgical oncologists and one plastic surgeon.

Surgical Technique

The surgical oncologist and the plastic surgeon perform the PM and IBR as a team in a 2.5-hour session. The operation is performed under general anaesthesia with the patient in a half supine position. The mastectomy is done through a vertical, peri-areolar incision, which extends from just above the nipple down to the submammarial fold. The breast including the superficial or subdermal fascia (creating thin skin flaps), the axillary tail, the nipple-areolar complex, and the fascia of the pectoral muscle are removed. The axillary nodes are not dissected in case of a prophylactic mastectomy or in case of in situ carcinoma as operation indication. The axillary nodes are resected through the vertical incision in case of invasive breast cancer as operation indication. After the mastectomy the silicone prosthesis is inserted by the plastic surgeon in a pocket created below the pectoral muscles with some extension to the space underneath the rectus abdominis and the serratus.

Development and Provision of Information

A working group consisting of two surgical oncologists, a plastic surgeon, a rheumatologist, a radiologist and a health psychologist developed information-modules. The modules contained (1) information about the surgical procedure and its possible complications (2) the different methods and surgical techniques of breast reconstruction (3) an account of IBR with the use of a silicone prosthesis;(4) the advantages of the use of a silicone prosthesis and a summary of the controversy over the use of the silicone implant (5) an explanation of the importance of attending check-ups and reporting complaints. Photographic illustrations were provided of various cosmetic results of IBR.

Routing of Patients

In general all patients undergoing oncological or prophylactic mastectomy are offered immediate breast reconstruction with a subpectorally placed silicone prosthesis. Some remarks for patient selection has to be made. Based on clinical experience this kind of reconstruction is not the method of choice for obese women or those with ptotic breast due to the disappointing cosmetic results. Moreover, based on previous research[17] women with radiation therapy of the chest wall are offered autologeous breast reconstruction because of the significant increased morbidity (capsular contracture and loss of prosthesis) of implant reconstruction in irradiated area. Finally skin-sparing mastectomy must be an oncological safe procedure. Therefor, women with T4 breast tumours are treated by regular mastectomy and are excluded from this study.

Patients with an increased risk for breast cancer were seen at the family cancer clinic and extensively informed of their risk of breast cancer, the screening schedule, the pros and cons of intensive surveillance and the possibility of prophylactic mastectomy (PM). Those patients requesting more information about PM were referred to one of the two surgical oncologist involved in the family cancer clinic.

All patients, who were interested in an immediate breast reconstruction following prophylactic or oncological mastectomy, were informed about this study. During a consultation with one of the two surgical oncologists, the aim and instruments (modules, questionnaire) of the study were explained to the patients. A separate consultation with the plastic surgeon followed for all patients in which detailed information about the method of reconstruction, the pros and the cons of the use of silicone prosthesis, and the expectations of cosmetic outcome was given. In this session photos of reconstructed breasts were provided.

Questionnaire

All patients received a self-report questionnaire after an interval of one-year following the operation. The questionnaire was divided into 5 sections dealing with (1) demographic details, (2) perceived advantages of IBR, (3) satisfaction with IBR, (4) information and, (5) quality of life, body image, and sexual functioning. Some items replicated questions used in previous research[22] or were part of existing scales.[23] The researchers of this study designed the other items.[24]

Analyses

Data were analysed using SPSS 10.0 for Windows (Statistical Package of the Social Sciences). Analyses used were frequency, Pearson's product-moment correlation, independent samples T-test, factor analysis and reliability analysis for scale construction. In addition stepwise regression analysis was used.

Scale Construction

All variables of interest in this study were based on the formation of the various items into scales. The criteria for the scale construction, based on methodological conventions and considerations of the results of the factor- and reliability analysis were Eigenvalue>1.0, factor loading>0.40, maximum variance accounted for, and Cronbach's alpha>0.60. All scales were separately checked for both patients with IBR after oncological mastectomy and prophylactic mastectomy. In Table 1, the results of the scale construction are presented. Quality of life was divided in physical and psychological complaint scales of the Rotterdam Symptom Checklist (RSCL).[23] Both contained 12 items. Body image was measured with items used by Bergman and van Dam.[22] Three examples of the 6 items used in this scale were: as far as my breasts are concerned I (1) feel no shame walking around naked (2) find it difficult to look at myself when getting changed and (3) find it difficult to touch my reconstructed breast. Answer categories were "very true", "true", "not at all true". The sexual functioning scale was made up of five items, which were specially constructed for this study on the basis of findings in the literature (Table 2). The answer categories were the same as for the body image items. The satisfaction score was based on the total score of seven items as reflected in Table 3. The reliability of the scale is α 0.75 and 42% of the variance is explained by these items. Information was based on the answers

Table 1. Details of the different scales: number of items, Cronbach's alpha, explained variance, and eigenvalue

Scale	Cases (n)	Items (n)	Cronbach's α	Explained variance (%)	Eigenvalue
Quality of life psychological	115	12	.90	50	5.87
Quality of life physical	114	12	.76	29	3.51
Body image	122	6	.69	45	2.73
Sexual functioning	82	5	.87	45	2.72
Satisfaction	108	7	.75	42	2.96
Information	103	5	.75	51	2.53
Prosthesis related complaints	109	4	.74	56	2.26
Cosmetics	92	4	.71	54	2.24
Femininity	100	3	.74	66	2.00
Depression	120	6	.64	39	2.30

Table 2. Items of the sexual functioning scale

Through IBR:	Agree % (all)	Agree % (prophylactic)	Agree % (cancer)
My sexual life can continue undisturbed	76	74	77
There is no need for my partner to feel inhibited in our sexual relation	75	77	72
I think that I have remained sexually attractive	65	69	60
I wanted to remain sexually attractive	64	65	63
No major changes have taken place in my sexual life	57	61	54

Table 3. Items of the satisfaction scale

Item	Yes % (all)	Yes % (prophylactic)	Yes % (cancer)
Would recommend IBR to other patients	94	98	90
Would do it again	88	88	88
Would recommend IBR with silicone prosthesis to other patients	84	84	84
Satisfied with reconstruction	80	87	74
Breast reconstruction meets expectation	68	77	61
Complaints about reconstruction	31	25	38
Would dissuade other patients from having IBR with silicone prosthesis	16	16	16

of five questions as presented in Table 4. Crohnbach 's α was 0.75 and 51% of the variance was explained by these questions. The specific prosthesis related complaints scale was made up of four items dealing with discomfort, pain, tension of the skin, and cold and stiff sensation of the skin of the reconstructed breast. The answer categories were "very true", "true", or "not at all true". The Cronbach's α was 0.75 and 56% of the variance was explained by these questions. For further analyses, the data on this scale were recoded in a high-complaint score and a low-complaint score. The maximum score was 11 and the minimum score was 4. A score between 4-7 was defined as high, whereas a score between 8-11 was defined as low prosthesis related complaints.

Furthermore scale constructions were made up for cosmetics (Table 5), femininity, and depression. The femininity scale was made up of three items, which were the answers to: The advantages of IBR are that I: (1) feel being a women again (2) feel having regained something of myself (3) have regained my feelings of femininity. The answer categories were "very true", "true", "not at all true". Three examples of the 6 items used in the depression scale were: (1) do you feel sad and down (2) do you have outbursts of crying (3) are you more irritable than before the operation.

RESULTS

Patients

Of the 139 patients, 124 (89%) completed and returned the questionnaire. Their age at operation ranged from 26.7 to 59.5 years (median 40.7 years, mean 41.0 years). The indications for mastectomy were invasive breast cancer in 52, extensive carcinoma in situ 11, and prophylactic mastectomy in 61 patients. These women were separated into 2 groups: the cancer group (n=63, age 26.9 – 67.6 years, median 43.5 years, mean 43.9 years) and the prophylactic group (n=61, age 26.7 – 57.7 years, median 38.6 years, mean 39,7 years).

Fifteen patients did not return the questionnaire. Their medical reports were checked to find a possible explanation. Ten patients underwent a prophylactic mastectomy and the other 5 an oncological mastectomy (breast cancer in 4 and carcinoma in situ in 1 patient). In 1 patient the prosthesis was removed due to complications. Another patient was treated with chemotherapeutics at the moment of receiving the questionnaire. The other 13 patients had no specific complaints or complications.

Advantages

The most important perceived advantage of IBR was not to have to wear an external prosthesis (overall 95%, prophylactic 100%, and cancer 90%) (Table 6). The advantages 'not to have to wear an external prosthesis' and 'to endure the amputation more easily' were significantly more mentioned in the prophylactic group (respectively chi-square=6.2, P=0.01, and chi-square=4.5,

Table 4. Items of the information scale

Need for more information about	Yes % (all)	Yes % (prophylactic)	Yes % (cancer)
Results of breast reconstruction	36	26	44
The use of silicone prosthesis	24	18	30
Dis/advantages of immediate reconstruction	23	15	32
Breast cancer and its treatment	15	13	18
Coping with specific problems and knowing where to find help	10	5	11

Table 5. Items of the cosmetic scale

My reconstructed breast(s) is/are	Agree % (all)	Agree % (prophylactic)	Agree % (cancer)
Artificial	65	59	69
Not similar	64	50	75*
Too high	33	19	41**
Skewed	20	19	21

* pearson chi-square 7,3 sig (2-tailed) p= .008
**pearson chi-square 5.2 sig (2-tailed) p= .03

Table 6. Advantages of immediate reconstruction

Advantages	Agree % (all)	Agree % (prophylactic)	Agree % (cancer)
Not to have an external prosthesis**	95	100**	90**
To avoid changes in sexual relation	76	74	77
To feel feminine again	75	75	75
To have an unchanged sexual relation with my partner	75	77	72
To wear a bra when desirable	66	75	62
To have the feeling of having something of my own again	66	63	70
To remain sexually attractive	65	69	60
To get rid of the cancer	63	71	57
To have more confidence	60	60	59
To feel myself again	59	66	53
To endure the amputation more easily**	50	60**	40**

** = significant (p<.05)

P=0.04). Six patients within the cancer group did not see 'not to wear an external prosthesis' as an advantage of IBR. Further in depth analysis showed that all these patients had more expectations of the result of IBR and had an asymmetric reconstruction.

Satisfaction with the Treatment

Patient's satisfaction with IBR by silicone prosthesis was measured in terms of seven questions (Table 3). There was no significant difference in the items of the satisfaction scale between the prophylactic and the cancer group. Almost all patients would recommend IBR to other patients (94%). Fifteen patients (12%) would never choose IBR again. Reasons given were: concerns about the possible complications associated with silicone gel implants (9), postoperative complications (4), and disappointing cosmetic result (1). One patient did not specify her disapproval for IBR with silicone prosthesis. Twenty patients (16%) would dissuade other patients from having IBR with silicone prosthesis. Eleven patients thought the choice for IBR with silicone prosthesis was too personally. Other reasons to dissuade women from having the treatment were postoperative complications (5), concerns about silicone prosthesis (2), disappointing cosmetic result (1), and preference for another method of IBR (1). Although one-third of the patients had complaints about the reconstruction, most patients were satisfied with the reconstruction and would undertake it again (further analysis about this finding will be presented in the next section). There was no correlation between the satisfaction factor or the 7 satisfaction items and who (myself/surgeon/together/others) the decision for IBR had made.

In Table 7 the correlation between satisfaction with IBR and psychological and physical quality of life, sexual functioning, specific complaints of the prosthesis and body image are presented. All, except body image, correlated significantly with satisfaction. The highest negative correlations were with cosmetics (r=-0.58), information (r=-0.45) and specific prosthesis related complaints (r=-0.39). The more specific prosthesis related complaints the patients had and the more information was needed, the less satisfied they were with IBR. In the stepwise regression analysis with satisfaction as dependent variable and psychological and physical quality of life, cosmetics, information and specific prosthesis related complaints of the prosthesis as independent variables, only the latter 3 variables entered the regression and explained 49% of the variance of satisfaction (R= 70; R-square= 0.49).

Overall body image correlated significantly with cosmesis (r=0.29, P=0.006), prosthesis related complaints (r=0.28, P=0.02) and depression (r=0.21, P=0.03). For the prophylactic group none of the scales correlated significantly with body image, but for the cancer group a significant relation was found for cosmesis (r=0.36, P=0.007), prosthesis related complaints (r=0.37, P=0.004), depression (r=0.26, P=0.05), and femininity (r=.32, P=0.02).

Prosthesis Related Complaints

Thirty-eight percent of the women in the oncological group and 25% in the prophylactic group had reconstruction related complaints (ns). Interesting differences were found between the

Table 7. Correlation between satisfaction and other scales

Scale	Satisfaction overall		Satisfaction prophylactic		Satisfaction cancer	
	r	p	r	p	r	p
Qual of life physical	.35	.000	.11	ns	.44	.001
Qual of life psychological	.24	.01	.22	ns	.22	ns
Sexual functioning	.26	.02	.07	ns	.21	ns
Prosthesis related complaints	-.39	.000	-.35	.01	-.35	.007
Cosmetics	-.58	.000	-.42	ns	-.61	.000
Information	-.45	.000	-.44	.003	-.44	.001
Body image	-.08	ns	-.17	ns	-.08	ns

Table8.Independentt-samplestestspecificcomplaintsofthebreastreconstruction(highandlow)andthedifferentscales

Scale	overall			Prophylactic group			Cancer group		
	t	Df	p	t	Df	p	t	Df	p
Qual of life physical	2.7	47.9	.009	0.6	20.9	ns	2.6	32.0	.01
Qual of life psychological	2.6	42.8	.01	1.3	12.4	ns	2.0	31.4	ns
Body image	-2.2	51.6	.03	0.4	27.1	ns	-2.7	32.0	.01
Sexual functioning	2.8	51.1	.007	0.8	14.7	ns	3.0	35.8	.006
Satisfaction	3.8	42.4	.000	1.8	14.0	ns	3.4	27.6	.002
Information	-2.7	50.0	.008	-2.6	12.4	.02	-1.5	38.5	ns
Cosmetics	-4.7	45.7	.000	-2.2	9.3	ns	-3.7	35.9	.001
Femininity	3.6	76.4	.001	1.4	22.8	ns	3.5	49.5	.001
Depression	-3.0	59.3	.004	-2.1	17.2	ns	-2.0	39.7	.05

Table 9. Correlation between satisfaction and information items

Item	Overall		Prophylactic		Cancer	
More information about	r	p	r	p	r	P
The use of silicone prosthesis	-.44	.000	-.32	ns	-.51	.000
Results of breast reconstruction	-.42	.000	-.44	.001	-.39	.002
Dis/advantages of IBR	-.32	.001	-.19	ns	-.37	.005

cancer and the prophylactic group as far as the relation between these complaints and the psychological profile of the patients were concerned. Recoding the total score of the answers into a high complaint and a low complaint group showed a significant influence of the specific prosthesis related complaints on the different scales for the whole group (Table 8). For the cancer group most scales showed a significant difference between the high and low complaint group, especially sexuality (t=3.0, df=5.8, P=0.006) and satisfacion (t=3.4, df=27.6, P=0.002). An interesting finding on the differences in the complaint groups for the cancer group, but not for the prophylactic group was for general satisfaction. Contrary to what one would expect (as indicated in the previous section), the high complaint group showed significant more satisfaction than the low complaint group. As can be expected for cancer patients because of the diagnosis of the illness, the physical quality of life score showed a significant difference, too (t=2.6, df=32.0, P=0.01). Other significant differences on psychosocial variables between the high and low complaint score for the cancer group, but not for the prophylactic group, were found for cosmetics (t=-3.7, df=35.9, P=0.001), body image (t=-2.7, df=32.0, P=0.01), and depression (t=-2.0, df=39.7, P=0.05). These differences showed a higher score for the low complaint group in comparison with the high complaint group. The only significant difference between the high and low complaint group found in the prophylactic group, but not in the cancer group, was for information (t=-2.6, df=12.4, P=0.02). For this result the low complaint group was more satisfied with the information provided than the high complaint group.

Information

Even though 95% of the patients obtained written information about IBR and silicone prosthesis, and 99% of the patients was informed about the use of a silicone prosthesis and 98% about the dis/advantage of silicone prosthesis, a quarter of the patients still had a need for more information (Table 4). The cancer group was more in the need of information than the prophylactic group, although not significantly. In general, most women (90%) were satisfied with the information that they had about how to cope with specific problems and where to find help.

The correlations between the information factor and the satisfaction and specific prosthesis related complaints were significant (r=-0.45, P=0.000 and r=0.32, P=0.001 respectively). This means, the less satisfied the patients were and the more complaints they had, the higher was the need for information. In Table 9 the correlation between satisfaction and the 3 of the 5 different information items are given. In the cancer group all these 3 items had a negative correlation, meaning, the less satisfied patients were with IBR, the higher was their need for more information about the use of silicone prosthesis (r=-0.51), the results of IBR (r=-0.39), and dis/advantages of IBR (r=-0.37). In the prophylactic group only satisfaction and more information about the results of IBR correlated significantly (r=-0.44, p=0.001).

DISCUSSION

In this study patients' satisfaction with, the treatment and information one year after mastectomy followed by immediate breast reconstruction with silicone prosthesis is evaluated. The examined patients were distinguished in two separated groups, those who underwent a prophylactic mastectomy and those who underwent a mastectomy for breast cancer. In the former group mastectomy is determined by balancing the negative effects of breast removal against the reduction of breast cancer incidence. Moreover, these women could choose between two treatment-options, regular surveillance versus prophylactic mastectomy, while the women with breast cancer had only one option. Furthermore, the decision making in both groups was different. A psychologically difficult decision-making process lengthens the time to operation in women with a prophylactic mastectomy. In the Daniel den Hoed Cancer Centre it takes half a year to one year after the patient is referred from the family cancer clinic to the definite prophylactic operation. In women confronted with the presence of breast cancer the time to operation is usually substantially shorter for oncological reasons.

Not to have the experience of an external prosthesis was the most important perceived advantage of IBR, which was significantly more agreed in the prophylactic group (overall 95%, prophylactic 100% and cancer group 90%, $p<.05$). This is in accordance with previous research[5,6,24], which indicated that the though of having to wear an external prosthesis was very threatening for women regarding sport and leisure activities and not being able to wear the clothes they want to. The 6 women (10%) within the cancer group, who did not see "not to wear an external prosthesis" as an advantage of IBR, had more expectations of the result of IBR and had an asymmetric reconstruction. Moreover these women were less satisfied and had more specific prosthesis related complaints. Perhaps these women would have had more benefit from an external prosthesis or delayed breast reconstruction than a disappointing immediate breast reconstruction.

In a report of Borgen 5% of the women had later regrets about the prophylactic mastectomy.[14] The most important factor that predicts an unfavourable outcome in this study was a physician-initiated discussion. In this study it was evaluated analogously if there was a relation between satisfaction with the IBR and the initiator for IBR. More than 50% of the women in the prophylactic group choose for IBR by themselves compared to 30% of the women in the cancer group. There was no relation between who had made the decision for IBR and satisfaction.

Overall, the patients in the underlying study were satisfied with their breast reconstruction with silicone implant. Almost all patients would recommend IBR to other patients (94%). Fifteen patients (12%) would never choose IBR with silicone prosthesis again, mostly because of the concerns about the possible complications associated with silicone prosthesis. It is claimed that silicone implants could introduce a rheumatoid autoimmune syndrome. At this moment a prospective study is carried out in the Daniel den Hoed Cancer Centre, in which all women are followed, who are operated since 1995 with subpectorally placed silicone prosthesis. In this study

women are checked regularly serologically and by questionnaire for Sjögren, rheuma/Raynaud related, and undefined complaints. The methods used in this study are already published in a retrospective study.[25] Awaiting the results of this prospective study the conclusions from the literature that there is no evidence for a silicone-related syndrome are conformed.[26-29]

Although 31% had reconstruction related complaints, 80% were satisfied with their IBR. These specific prosthesis related complaints were highly correlated with satisfaction (r=-.39, p=0.000). Moreover, this was one of the 2 scales showing significant results with the satisfaction scale in both the prophylactic and cancer group. On the whole more the prosthesis related complaints were scored for the cancer group than for the prophylactic group. A closer look at the results of the t-tests between the complaint groups and the different scales also showed more significant differences for the cancer group than for the prophylactic group. The results as far as sexuality and femininity are concerned, showed that these female domains were more affected by the occurrence of both cancer and physical complaints. Maybe these two together were too much stress for a patient to cope with, while at the same time trying to come to terms with a mutilation of the female breast - the pillar of both sexuality and femininity. This explanation was supported by the results of the cosmetic and body image scales, because these domains were affected by the whole group of cancer patient irrespective of the strength of their physical complaints. The result that the lower complaint group had a higher depression score for women with cancer was also interesting. A possible explanation for this could be that physical complaints detract attention away from the psychological process of dealing with the cancer diagnosis. An absence of these complaints could mean that one has to confront the anxiety and uncertainty of this life threatening disease. Feelings of depression were still quite common in patients a year after their operation.[30,31]

These results also showed that the quality of the information provision about the reconstruction was more important for the prophylactic group with low physical complaints than for the cancer group. An explanation for this could be that these women had less stress because of fewer complaints and no cancer diagnosis to come to terms with. In the light of stress theory[32], this could mean more concentration for other domains such as information.

Furthermore, the non-significant correlation between satisfaction and body image was interesting and contradicts previous research findings that breast reconstruction in general and immediate breast reconstruction in particular have a significant influence on body-image.[6,18,19,33-35] A closer look at the body image scale shows a significant correlation with cosmetics, prosthesis related complaints, depression, and the femininity for the cancer group but none for the prophylactic group. A possible explanation for this can be found in the scale construction. In this study body image was measured with items used by Bergman and van Dam.[22] In their study, only women with mastectomy for breast cancer were included. Probably, this scale was not applicable to the population of women with prophylactic mastectomy. However, in previous research[24] a significant correlation between satisfaction and body image was found. The reason for this contrary result is interesting. Looking at the items of the various

scales it was clear that cosmesis, prosthesis related complaints, depression and femininity were more focussed on the body (the breasts) than the satisfaction scale. The correlations between these scales and satisfaction were significant, especially for the cancer group. So a possible explanation could be that the absence of a significant result between body image and satisfaction was due to the choice of the scales for this study.

In previous research[17,36] it was indicated that IBR with a subpectorally placed silicone prosthesis was with considerable complications, especially in women who had had radiation therapy of the thorax previous or after IBR. In particular, capsular contracture around prostheses situated in the radiation field was significantly increased.[17] In this study the group women with radiation therapy was too small to compare satisfaction in women with or without radiation therapy and IBR. On the other hand the most common delayed complication of IBR with a subpectorally silicone prosthesis was capsular contracture which occurred in 21% of the reconstructions leading to surgical intervention in 88%.[17] Capsular contracture could result in hardening, tightness, mild-to-severe pain and deformity of the breast. In other words these symptoms were in accordance with the items of the prosthesis related complaints. Indirectly we could say that it is likely that complications may have an impact on satisfaction with IBR.

The unexpected finding of this research was the significant finding that the high complaint group showed more satisfaction than the low complaint group. A possible explanation for this might be found in Festinger's Cognitive Dissonance Theory.[37] This theory clarifies the difficulty people experience when living with two conflicting constructs. Having made the choice for breast reconstruction was positive, enduring physical complaints was negative. If the woman would indicate that she was dissatisfied with the reconstruction, she had to admit that she had made the wrong choice. Unless the reconstructive breast is removed, this leads to a state of dissonance, which is psychologically uncomfortable and quite stressful for a person. If the woman states that she is nonetheless satisfied with the reconstruction, her cognitive state is consonant and less stressful.

Since the need for more information about silicone prosthesis and breast reconstruction was compared in a former published study[24], it can be concluded that the need for more information is weakened. The patient sample can explain this: in the present study 50% of the women had a prophylactic mastectomy, compared to 12 % prophylactic mastectomies in the former study. In the present study the cancer group was more in need for information, although not significant. Moreover, satisfaction was significantly correlated with 3 information items in the cancer group conform the former study.[24] In the prophylactic group only one information item correlated significantly. This can be explained by the difference in decision-making time-interval. While a women with a high risk for breast cancer has several contacts with different specialist (genetics, oncologist and surgeon) during a period of several months in which a thoughtful decision can be made for prophylactic mastectomy and IBR, a women with breast cancer has only several weeks. In other words the high-risk women have more time to get the information they wanted and have more time to think about the treatment they are going to chose for. The

cancer patients, on the other hand, need more effective information for important decisions in a shorter time interval.

CONCLUSIONS

The main advantage of IBR is 'not to have to wear an external prosthesis', which is significantly more agreed in the prophylactic group. More than 50% of the women with a prophylactic mastectomy choose IBR themselves. This is significantly more than in women with an oncological mastectomy, for whom the choice for IBR is made primarily by the surgeon. Satisfaction is not related to the decision-maker of IBR (patient/ surgeon/ together).

Although many women (31%) have breast reconstruction related complaints, the majority (80%) is satisfied with IBR after mastectomy. There is no significant difference in satisfaction between the prophylactic group and the cancer group. Overall satisfaction is mostly influenced by cosmetics, information, and prosthesis-related complaints. Especially prosthesis related complaints are important for both the prophylactic and the cancer group.

It is very important to inform women undergoing IBR with a subpectorally placed silicone prosthesis about the possible specific prosthesis related complaints.

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CHAPTER IV.1

Morbidity of immediate breast reconstruction (IBR) after mastectomy by a subpectorally placed silicone prosthesis: the adverse effect of radiotherapy

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European Journal Of Surgical Oncology 2000;26:344-350

ABSTRACT

Objective: This study evaluates the incidence of local complications after immediate breast reconstruction (IBR) following mastectomy with a subpectorally placed silicone prosthesis, with emphasis on the effect of radiation treatment on IBR.

Methods: The medical records of 100 women, who underwent a mastectomy followed by IBR with a subpectorally placed silicone prosthesis at the University Hospital Rotterdam/Daniel den Hoed Cancer Center, between March 1990 and March 1995, were reviewed. Thirteen prostheses were implanted prior to radiation treatment, and 15 prostheses were implanted after irradiation of the chest wall.

Results: Early complications were seen in 15% of the IBR and were more often in irradiated women. At long-term follow-up, the most common complication was capsular contracture (21%). This occurred significantly more around prostheses placed in a previously irradiated area ($P<0.0005$), or which were irradiated after IBR ($P=0.001$). Loss of prosthesis was seen in 11 cases, and was significantly ($P<0.005$) more in irradiated women (n=5: 18%) compared to women who were not irradiated (n=6; 7%).

Conclusions: Complications after IBR with a silicone prosthesis were more common in women who were treated with radiotherapy prior to or after IBR following mastectomy than in women who were not irradiated. In particular, capsular contracture around a prosthesis placed in a previously irradiated area was significantly increased. The use of musculocutaneous flaps, such as the transverse rectus abdominis muscle or latissimus dorsi flap, is preferable for reconstruction of previously irradiated breasts. There is no indication to remove the prosthesis before radiation therapy of the chest wall.

INTRODUCTION

In recent years, the surgical treatment of breast cancer has significantly improved with regard to the reduction of mutilation. In Halsted's 'radical' mastectomy, both the pectoral muscles were removed en bloc with the breast and ipsilateral axillary lymph nodes; later on, Patey and Madden introduced the modified radical mastectomy, in which the pectoral muscles were preserved. Nowadays, breast conserving therapy (BCT) combining lumpectomy and axillary lymph node dissection, followed by radiation of the breast, is commonly used. However, for oncological reasons, BCT is not recommended for all patients. Depending on size, location or pathological features of the tumour, mastectomy can be the therapy of choice. Local recurrence of breast cancer after BCT can also be an indication for mastectomy. In these cases, breast reconstruction may be the means to improve cosmesis and reduce mutilation. Breast reconstruction can either be undertaken by using silicone implants or autologous tissue.

Since 1962,[1] silicone breast implants have become widely used for both cosmetic and reconstructive surgery. After their introduction, silicone implants became a topic of concern in the medical literature, as well as in the lay press,[2-4] with both systemic and local complications reported. Since 1994, several cohort studies have described the induction of an atypical connective tissue disease or of rheumatic complaints by silicone breast prosthesis.[5-8] In contrast to these reports, recently published studies could not find a relationship between silicone breast implants and these syndromes.[9-14]

Local complications after silicone implantation, such as capsular contracture, wound infection, implant rupture or leakage, seem to be an important problem. A complication rate ranging from 24 to 64% has been reported.[15-18] Risk factors associated with an increased complication rate are smoking, obesity, age at implantation,[15] breast reconstruction (vs augmentation) as indication for implantation,[16-17] and the use of smooth rather than textured implants.[18] Since 1990, the Department of Surgical Oncology of the Daniel den Hoed Cancer Center has performed immediate breast reconstruction (IBR) after mastectomy using a subpectorally placed silicone prosthesis. In this study, we present the occurrence of local complications after immediate breast reconstruction, and in particular the effect of radiotherapy on IBR.

PATIENTS AND METHODS

All women who underwent a mastectomy followed by immediate breast reconstruction with a subpectorally placed silicone prosthesis, non-textured (Eurosilicone, Cergy, France) (Fig. 1) at the University Hospital Rotterdam/Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, from March 1990 until March 1995, were included in this study. The mastectomies with or without axillary lymph node dissection were all performed by a general surgeon in

close cooperation with the plastic surgeon. Who reconstructed the breast with a subpectorally placed silicone prosthesis.

All medical records of these patients were reviewed. Age, medical history, radiation therapy, radiation dose, chemotherapy, time intervals between reconstruction and adjuvant therapy, post-operative complications and follow-up were collected from the medical records.

The Baker's classification[19] was used for grading the severity of capsular contracture: Grade I, the reconstructed breast feels as soft as breast not operated on; Grade II, the breast is less soft: the implant can be palpated, but is not visible; Grade III, the breast is firmer: the implant can be palpated easily, and it can be seen; Grade IV, the breast is hard, tender, painful, and cold. Distorsion is often marked. Wound infection was defined as 'minor' in case of erythema of serous discharge and as 'major' in case of purulent discharge.

Radiation Therapy

Radiation therapy was administered using 6-10 MeV linear accelerators. After BCT, patients received 45-50 Gray (Gy) on the whole breast, by means of tangential fields. This was followed by a boost dose of 16-20 Gy on the primary tumour site. Fraction size was 2.0 to 2.5 Gy daily, four to five fractions a week. The same technique and dose was used following modified radical mastectomy and immediate reconstruction, in case of tumour resection with microscopically involved margins or in case of local recurrence. Treatment of the reconstructed thoracic wall was usually combined with irradiation of the axilla, depending on histological features. Only in the case of microscopically marginal resection of the primary tumour, was boost dose of 10-20 Gy applied locally.

Statistical Analysis

Pearson's chi-squared test and Fisher's exact test were used to test for differences in proportions between subgroups. Univariate Cox regression analysis with time-dependent covariates was used to assess risk factors for the time to occurrence of first post-operative complications, and capsular contraction in particular. The variables that were significant in the univariate analysis were also included in a multivariate Cox regression. All reported P-values were two-sided, and a significance level α=0.05 was used. Kaplan-Meier curves of the time between surgery and post-operative complications were reconstructed.

RESULTS

Patient Population

One hundred women underwent 115 mastectomies followed by immediate reconstruction with a subpectorally placed silicone prosthesis, unilateral mastectomy was performed in 85 and bilateral mastectomy in 15 women. The indications for mastectomy are given in Table 1.

Table 1. The indication of the mastectomy

Indication of mastectomy	Unilateral (n=85)	Bilateral (n=15)	Total
Carcinoma	47	12	59
Extensive DCIS*	25	-	25
Recurrence after BCT	9	2	11
Paget's disease	3	-	3
Prophylactic	1	16	17
Total	85	30	115

* Extensive ductal carcinoma in situ
n number of women

Table 2. Complications after breast reconstruction with a silicone prosthesis

Complication	Early complication (<6 weeks*)		Late complication (>6 weeks)*	
	n	(**)	n	(**)
Infection	7	(3)	3	(2)
Wound necrosis	5	(4)	-	-
Bleeding	3	(3)	1	(1)
Haematoma	2	(1)	-	-
Luxation	-	-	5	(4)
Capsular contracture	-	-	24	(21)
Total	17 (15%)	(11)	33 (29%)	(28)

* after surgery
** number of complications leading to surgical intervention

The median age at reconstruction was 46 years (range 25-71 years). The median follow-up time was 30 months (range 7-67 months). During follow-up, three patients died, 7, 32, and 42 months after IBR, respectively, due to progressive metastatic disease.

Of the 100 women, 28 patients received radiotherapy before or after surgery; 15 patients were treated previously for breast cancer by BCT, involving radiation of the breast. The median radiation dose given was 65 Gy (range 45-70 Gy). The interval between BCT and ablatio of the breast with IBR ranged from 12 to 97 months (median 43 months). The indication for secondary mastectomy of the breast was recurrence of disease (11), followed by prophylactic mastectomy (2), ductal carcinoma in situ (DCIS) (1) and Paget's disease (1).

Thirteen women were treated with radiation therapy of the chest wall after IBR, because of the histological features of the axillary lymph nodes (apical lymph node metastasis, more than five lymph nodes with metastatic disease and extra nodal tumour growth) in six patients, and mastectomy with microscopically positive resection margins in four patients. Two patients developed a local recurrence, 14 and 19 months after IBR, and one patient had a solitary supraclavicular lymph node metastasis 1 year after IBR. These three patients were treated with radiotherapy of the chest wall including the prosthesis. The median radiation dose given

in these 13 patients was 46 Gy (range 30-70 Gy). The median time interval between breast reconstruction and radiation therapy was 3 months (range 1-19 months).

Twenty-seven patients received chemotherapy after IBR; 22 of these patients had microscopic evidence of axillary lymph node metastasis and four patients developed metastatic disease. One patient, whose indication for IBR was a local recurrence after BCT, requested and received chemotherapy.

Complications

One hundred and fifteen breast reconstructions in 100 women were monitored for complications over a median follow-up period of 30 months (range 7-67 months) after IBR. In 71 reconstruction (62%) no complications were observed.

Within 6 weeks after surgery, 17 early complications were seen, leading to surgical intervention in 11 cases (Table 2). The most common early complication was infection. During the total follow-up period there were 10 infection: five minor, all treated sufficiently with oral antibiotics, and five major infections, all leading to loss of prosthesis. Twenty-seven women received chemotherapy following IBR. Only one patient had a low-grade infection of the skin above the prosthesis during the first cycle of chemotherapy, which was sufficiently treated with oral antibiotics.

At long-term follow-up, capsular contracture was the most common complication and occurred in 21% of the reconstructions (Table 2). According to the Baker classification, there were seven grade II (Fig. 1), 12 grade III (Fig. 2) and five grade IV (Fig. 3) capsular contractures. Capsular contracture appeared 5 to 46 months after IBR (median 17 months). None of the patients who had an infection in the post-operative period developed a capsular contracture. In two of the six prostheses (33%) in patients who had haematomas of post-operative bleeding, capsular contracture developed, compared to 20% (22/109) in the group without post-operative haematomas or bleeding (P=0.60).

Figure 1. Non-textured silicone prosthesis, used for breast reconstruction in all women participating in this study

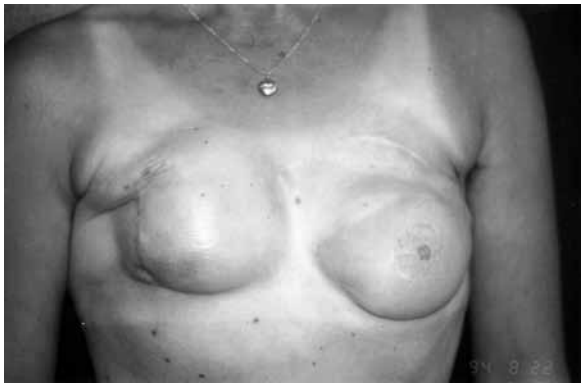

Figure2.CapsularcontracturegradeIIIwasacquired 2yearsaftermastectomyandIBRoftherightbreast forrecurrenceofbreastcancer,6yearsafterbreast conservingtherapy.AdelayedTRAMreconstruction andnipple/areolareconstructionwasdoneafter modifiedradicalmastectomyoftheleftbreastfor breast cancer

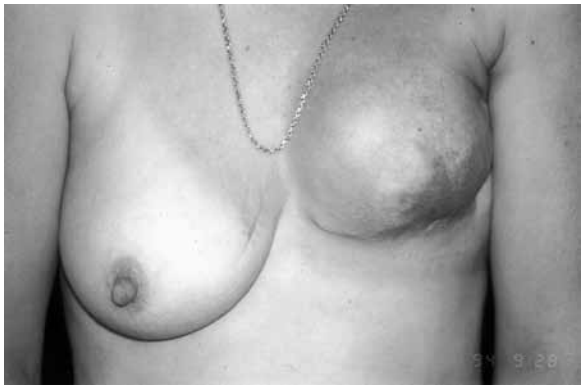

Figure3.CapsularcontracturegradeIVwasseen1 yearaftermodifiedradicalmastectomyandIBRof theleftbreastforbreastcancer.Adjuvantradiation ofthereconstructedthoracicwallwasgivenbecause ofmicroscopicallyinvolvedresectionmarginsofthe tumour

Considering the whole follow-up period, there were 48 complications, leading to loss of prosthesis in 11 cases (10%), due to infection (n=5), capsular contracture (n=4) or wound necrosis (n=2). Although capsular contracture was the most common complication, this did not contribute to loss of prosthesis as much as infection or wound necrosis. Loss of prosthesis was significantly seen more often in prostheses that were implanted prior to or following radiation therapy (P<0.005) (Table 3). The actuarial probability to loose a prosthesis within 3 years was 10% (standard error 3%).

Personal discomfort, which was not considered as a complication, led to removal of the implant in one patient.

Age in relation to Complications

Fifty patients (57 IBR) were 45 years or younger, and 50 patients (58 IBR) older than 45 years. The post-operative complication rates were comparable for both age groups: the actuarial probability of complications was 28% after 1 year and 50% after 3 years in the younger patient group, while these probabilities were 24 and 37% in the older patient-group (P=0.28).

Table 3. Complications leading to loss of prosthesis in relation with radiation therapy

Complication*				No RT		RT	
	N	n	(%)	n	(%)	n	(%)
Infection	10	5	(50)	3		2	
Capsular contracture	24	4	(17)	2		2	
Wound necrosis	5	2	(40)	1		1	
Total	39	11	(28)	6	(7)	5	(18%)

* Complication leading to loss of prosthesis
N total number of complication
n loss of prosthesis due to complication

Table 4. The relation between radiation therapy and complications

Radiotherapy (RT)	N	Early complication		N	Capsular contraction	
		n	(%)		n	(%)
No RT	100*	13	(13)	87*	10	(11)
RT before IBR	15	4	(27)	15	9	(60)
RT after IBR	-	-	-	13	5	(39)
Total	115	17	(15)	115	24	(21)

* no RT before IBR
** no RT before, nor after IBR

Table 5. Percentage of complications following breast reconstruction (TRAM flap or silicone implant) in patients irradiated before or after reconstruction, respectively

Radiation therapy before breast reconstruction						
	n	Total complications	Fat necrosis	Major infection	Fibrosis	Failure
TRAM						
Williams[37]	108	25	18	7	0	0
Kroll[38]	66	33	-	-	0	6
SILICONE						
this study	15	80	-	7	60	20
Radiation therapy after breast reconstruction						
	N	Total complications	Fat necrosis	Major infection	Fibrosis	Failure
TRAM						
Williams[37]	19	53	25	5	32	0
Hunt[40]	19	26	11	5	11	0
SILICONE						
this study	13	46	-	0	36	15

Radiation Therapy in relation to Complications

Twenty-eight women received radiation therapy (RT); 15 reconstructions were done in irradiated area (RT before breast reconstruction) and 13 prostheses were situated in the radiation field (RT after breast reconstruction). In Table 4 the relation between radiation therapy and complications is shown. The incidence of early complications was higher, though not statistically significant, in the group of women who received radiation therapy of the breast in the past (27% (4/15), compared to 13% (13/100) in breasts without irradiation P=0.23).

Capsular contracture, the most common complication, was seen significantly more often around prostheses implanted in a previously irradiated area (P<0.0005). Moreover, irradiation after IBR was associated with a significant increase of capsular contracture (P=0.001). In the multivariate Cox regression, taking both radiotherapy prior and after implantation in to account, the hazard ratio of capsular contracture around prostheses placed in the radiation field (RT prior to reconstruction) was 7.5 (95% confidence interval (CI) 3.4-16.6) and 6.5 (95% CI 2.7-15.8) in prostheses irradiated after IBR. There does not seem to be a relation between gradation of capsular contracture and radiotherapy.

DISCUSSION

Implantation of a silicone prosthesis has become an important method for reconstruction of the breast after mastectomy. Compared to breast reconstruction with musculocutaneous flaps, such as the latissimus dorsi and the rectus abdominous flap, the insertion of a silicone implant beneath the pectoralis major is a relatively simple technical procedure. Furthermore, on theoretical grounds, its subpectoral insertion offers better local oncological screening in comparison with the suprapectorally placed musculocutaneous flap reconstructions.

In this study, we evaluated the incidence of complications after immediate breast reconstruction with silicone implants. This procedure has a high complication rate of 40%, leading to an actuarial probability of 10% to lose the prosthesis within 3 years. This is comparable to other studies.[15,16,20] Age at time of surgery was not associated with an increase of complications. Although capsular contracture was the most common complication, this did not contribute to loss of prosthesis to as great a degree as infection or wound necrosis. The main reason for removing the prosthesis was infection. However, there is no indication to remove a silicone prosthesis before adjuvant chemotherapy following IBR in order to prevent septic complications during the chemotherapy regimen. In this study, only one patient had a low-grade infection of the skin above the prosthesis during the first course of chemotherapy, which was sufficiently treated with oral antibiotics.

Complications occurred more commonly in reconstructions in women with a history of radiation therapy of the breast or in women who received chest wall radiation after IBR.

In particular, capsular contracture around prostheses situated in the radiation field was significantly increased.

Experimental studies have indicated that the presence of a silicone gel implant does not compromise the treatment of breast cancer by irradiation.[21-23] However, radiation did have some influence on the prosthesis. The implant became less formable following irradiation.[21] Several clinical studies, dealing with breast conserving therapy in women with augmentation mammoplasty, describe the effect of radiation therapy on the complication rate and cosmesis. Some authors have confirmed the rather poor cosmesis due to fibrotic changes and capsular contracture around the prostheses after radiotherapy.[20-26] In contrast, others have reported good cosmetic results.[27-29]

The aetiology of capsular contracture, resulting in hardening, tightness, mild-to-severe pain and deformity of the breast is not completely understood. Peri-prosthetic bacterial contamination may be associated with a high incidence of capsular contracture.[30-32] In this study, none of the post-operative wound infections resulted in developing of capsular contracture. A number of studies suggest that haematoma is a predisposing factor as well.[18,33,34] In the present study, haematomas of post-operative bleeding were followed by a somewhat higher, although not statistically significant, incidence of capsular contracture.

The silicone prosthesis used in this study is non-textured. Smooth, rather than textured implant surface have also been implicated as causes of capsular contracture.[18,35-37] Therefore, we introduced the textured silicone prosthetic for breast reconstruction in our clinic in 1998.

Little information is found in the literature regarding breast irradiation in patients with mastectomy and IBR using a subpectorally placed silicone prosthesis. Two case-studies concluded that breast reconstruction is feasible and well tolerated with regard to cosmesis after irradiation.[38,39] Kuske et al.[20] evaluated 66 women who received breast reconstruction followed by radiation therapy (40 to 50 Gy). Of the 71 breast reconstructions, 26 were done by subpectorally placed silicone implants, supplied by many manufactures and constructed of various materials. The complication rate within this group was 46%. The other 45 breast reconstructions were tissue expanders (25), latissimus dorsi flap in combination with a silicone implant (11), TRAM flap (eight) and gluteal flap (one). Although the complication rate was highest in the transverse rectus abdominous flap (63%), this type of reconstruction had the best cosmesis scores, followed by the permanent silicone prosthesis. The authors concluded that radiation therapy and breast reconstruction are not incompatible, although cosmetic failure and complication rates are significant. In concordance with other studies they advised a TRAM flap as breast reconstruction of first choice in irradiated patients.[40-43] Recently, Roy et al.[44] gave a review of 111 patients with post-mastectomy reconstruction using the latissimus dorsi flap in combination with a prosthesis (saline- or silicone filled). The overall complication rate was 44%. Capsular contracture developed in 13%. There was no effect of radiotherapy on the incidence of implant-related complications.

In our study, previously irradiated patients with silicone breast implants are at higher risk for complications, especially capsular contracture, in comparison to patients who underwent TRAM flap breast reconstruction (Table 5). Therefore, we conclude that the use of myocutaneous flaps is preferable for reconstruction of previously irradiated breasts. These findings have resulted in a change of our policy for the treatment of irradiated patients with IBR. In stead of using a subpectorally placed silicone prosthesis, we have decided to reconstruct the breast using myocutaneous flaps, TRAM or latissimus dorsi flap (the latter in combination with a prosthesis).

Patients who received radiation therapy after breast reconstruction with a silicone implant are also at higher risk of complications. However, there is no indication to remove the prosthesis before radiation therapy, as post-radiation loss of prosthesis in this study is only 15% (2/13). The complications rate following breast reconstruction with TRAM flap or silicone prosthesis is similar (Table 5).

In conclusion, complications after breast reconstruction, and especially IBR with a subpectoral silicone prosthesis, occur more frequently in irradiated patients than in non-irradiated patients. Adequate information on possible complications should be given to these patients whatever the applied technique for breast reconstruction may be. Finally, we recommend the use of musculocutaneous flaps for breast reconstruction in previously irradiated patients.

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CHAPTER IV.2

Mastectomy by Inverted Drip Incision and Immediate Reconstruction (MIDIIR): Data from 510 cases.

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Accepted for publication Annals of Surgical Oncology

ABSTRACT

Objective: Immediate reconstruction of the breast can be performed in selected cases after mastectomy for breast cancer or after prophylactic mastectomy in patients with a high risk to develop breast cancer. In spite of the frequency with which these procedures are performed, data from large series of subpectoral implantation of silicone prostheses in combination with a skin saving approach are lacking.

Methods: In this retrospective study, data on complications and late surgical interventions in 356 patients who underwent 510 mastectomies with an inverted drip incision and immediate reconstruction (MIDIIR) were analysed to determine potential prognostic factors of early complications.

Results: In 82% of the MIDIIR the postoperative course was uneventful. In 18% the complications were infection (32 cases), bleeding (31 cases), necrosis of the skin flap (29 cases), and protrusion of the prosthesis (20 cases) resulting in surgery in 9, 12, 15 and 20 cases, respectively. At the end of the follow-up period, 30 (6%) prostheses were definitively removed. Age, size of the prostheses, radiotherapy, previous lumpectomy and indication for mastectomy were not significant factors for the prognosis of early complications.

Conclusion: With the right technique and indication MIDIIR is a very safe procedure and should be one of the surgical skills that can be offered in the overall management of patients with, or at high risk for, breast cancer.

INTRODUCTION

In the 19th century mastectomy was performed only in patients with bulky or ulcerating breast cancers, and the local control rate was very low. For instance, between 1867 and 1876 Billroth performed 170 mastectomies and the local recurrence rate was 82%.[1] When Halsted introduced the principle of radical surgery for breast cancer by combining a simple mastectomy with resection of both pectoral muscles and an en-bloc axillary node dissection (also for less advanced stages), the local control rate improved considerably. Between 1889 and 1894 in 50 patients the rate was 6%, but later increased to 32% when the same group was studied again in 1931.[2,3] This radical mastectomy principle was subsequently modified, first by saving the minor pectoral muscle and later by saving both pectoral muscles, without loss of local control being more than 90%.[4-7]

In selected patients radiotherapy of the chest wall is indicated; e.g. in case of irradical resection of the chest wall and extensive axillary lymph node metastases.[8] In recent decades attention has focused on improving other important issues in breast cancer patients; e.g. from a surgical viewpoint, by improving cosmesis. Nowadays it is generally accepted that conservative surgery and radiotherapy is an excellent alternative for modified radical mastectomy, also leading to better patient acceptance and psychosocial effects.[9,10] Subsequent analyses of trials with breast conserving therapy (BCT) resulted in better selection criteria for patients with a relatively high local recurrence rate and thus not recommended for BCT (e.g. related to irradical lumpectomy, age, extensive DCIS).[11,12]

Patients that are recommended to undergo a mastectomy can be offered a delayed or immediate breast reconstruction. (figure I) The main disadvantage of delayed reconstruction is the period of unnecessary mutilation, and the relative loss of skin that also has to be reconstructed.

Immediate reconstruction of the breast must be a safe oncological procedure that does not lead to an increased number of local recurrences compared with mastectomy alone. Following a Medline search, Malata and colleagues concluded that there is no evidence that immediate reconstruction is associated with higher recurrence rates or interferes with the physical examination during follow-up.[13] Of all available methods for immediate reconstruction, the reconstruction with a subpectoral placed prosthesis allows the same properties in chest wall palpation as without a prosthesis. The recurrence rate seems to correlate with the tumor stage and biological properties of the breast cancer.[14] Outcome was very similar for pre- and postmenopausal patients and seemed independent of lymph node status.[15] Moreover, an immediate breast reconstruction was shown not to influence subsequent therapy, because adjuvant chemotherapy does not increase the complication rate.[16]

Whether the skin sparing incision is safe has not yet been investigated in a randomised phase III study; published data are mainly based on personal experience. Carlson and colleagues compared their series of 188 patients undergoing skin sparing mastectomy with a historical control group of 327 patients with mastectomy alone and concluded that the local recurrence rate was similar in both groups (4.8 vs 9.5%, respectively, after a median follow-up of 41

months).[17] This conclusion was confirmed by others: Slavin et al. investigated 114 native skin flaps and found no evidence for the presence of ducts in the resection margins, while Gabka et al. stressed the need for experience in performing this procedure to achieve these results.[18,19]

Developments in the clinical genetics of breast cancer and the discovery of the BRCA genes, gives women at high risk a choice between intensive surveillance or prophylactic mastectomy. In our clinic, women who choose for prophylactic mastectomy are offered an immediate breast reconstruction.

Whereas Halsted used a vertical scar, this was later changed to a horizontal scar for modified radical mastectomy because this horizontal approach enables the surgeon to amputate the breast with wide exposure of the lateral region and the axilla. The wound is usually tailored by reducing the lateral and medial dog ears, and produces a "nice flat appearance". Nevertheless, this scar is ugly and creates some important problems in delayed reconstructive surgery.

In 1990, when our department started with immediate breast reconstruction by placement of a subpectoral silicone prosthesis after mastectomy, the matter of the scar was also extensively discussed. Since we were troubled by the transverse scar we changed our approach. In 1992, for cosmetic reasons we decided to use Halsted's original vertical scar but with some modifications; the so-called skin sparing "inverted drip incision".

The aim of the present study is to investigate the surgical results (complications and/or corrections) of Mastectomy by an Inverted Drip Incision and Immediate Reconstruction (MIDIR) and compare these results with other data from the literature.

PATIENTS AND METHODS

Surgical Technique

The operation is performed by a surgeon and a plastic surgeon with the patient in semi sitting position, the elbow in flexion and the hand positioned low on the back. The previous aspiration tract or the in/excisional biopsy should have been performed in the future vertical region which

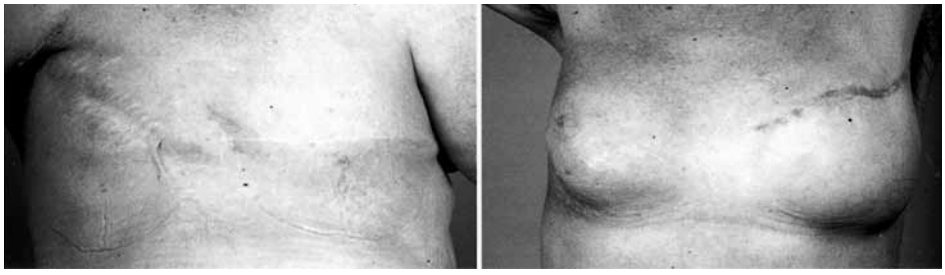

Figure 1. Photographs of two patients illustrating the surgical history of mastectomy for breast cancer. Left photograph: the right side shows the Halsted incision and the left side shows a modified mastectomy. Right photograph: The right side shows a lumpectomy and radiotherapy for breast saving therapy and the left side shows an immediate reconstruction with a subpectoral prosthesis after mastectomy

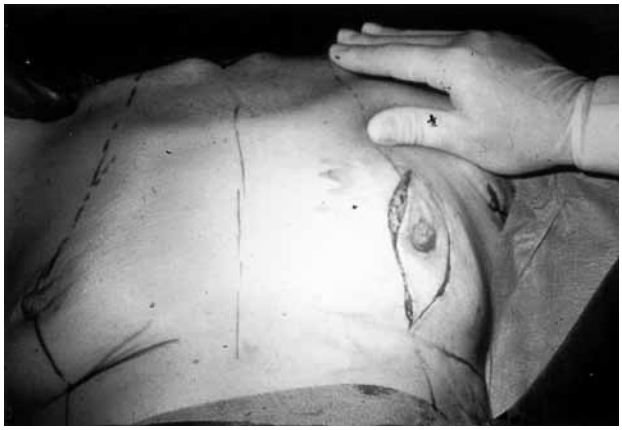

Figure2.Theinverteddripincision.Starting witharoundedgejustabovethenippledown to1to2cmabovetheinframammaryfoldwith a sharp edge

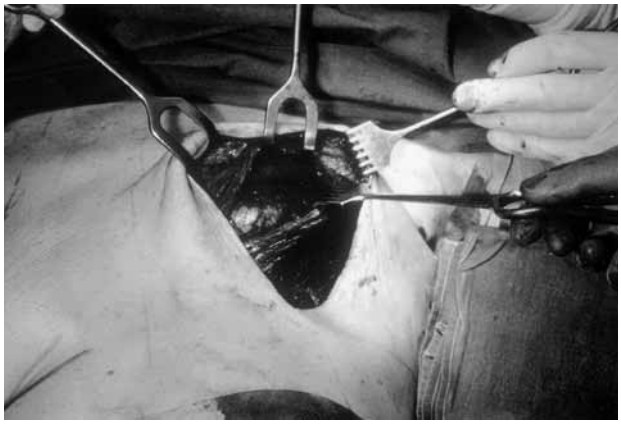

Figure3.Theenvelopetechniqueshows crossingoftheskinincisionandthepectoralis incision.Subpectoralprosthesiswithextension undertherectusabdominismuscleandserratus muscles

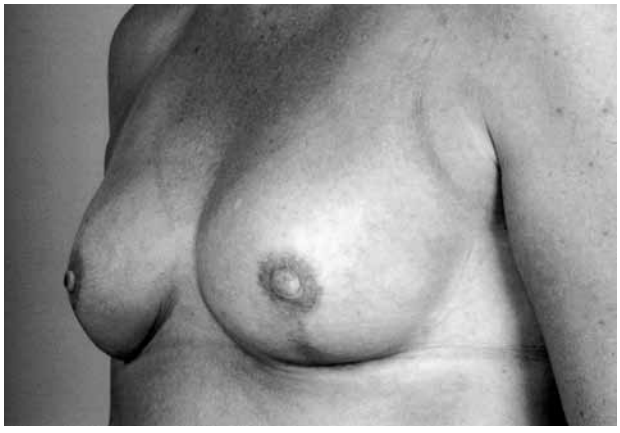

Figure4.Bilateralprophylacticmastectomy withinverteddripincisionandimmediate reconstruction(MIDIIR)anddelayednipple reconstructionasperformedinourclinic.

includes the nipple[8]. The incision extends from just above the nipple down to 1 to 2 cm above the inframammary line (figure II). If the previous scar of a lumpectomy is too far away to include the vertical incision, a separate incision is made to remove the scar in continuity with the breast tissue. Although somewhat less accessible, a mastectomy is then performed using a fiberoptic headlight and dissection by diathermia in the avascular plane. Dissection of the axillary nodes for staging purposes can usually be done through this incision, but a separate incision may be needed if there is inadequate access to the axillary vein. After mastectomy a subpectoral silicone implant (Cristalline Paragel®, laboratoire Eurosilicone, Apt, France) ranging from 150 to maximum 600 ml is inserted through the greater pectoral muscle. Great care is taken to dissect sufficiently far down under the origo of the rectus abdominis muscle and laterally under the serratus muscles, and sometimes even part of the pectoralis minor. Two suction drains are placed, one beneath the pectoral muscle and the other under the skin layer. The skin is closed in layers, without correcting the dog ears. Patients are scheduled for a 5-day stay. The suction drains are removed after production of 20 cc or less drain fluid on two consecutive days. The operation is performed under prophylactic antibiotic and subcutaneous anticoagulant administration. Nipple reconstruction is offered after 6 months.

Study Population

All women who underwent a MIDIIR at the Erasmus Medical Center/Daniel den Hoed Cancer Clinic between January 1992 and August 2001 were included in this study. All medical records of these patients were reviewed (mean follow-up was 63 months; range 3-116 months). For logistical reasons the postoperative course was divided in two periods: an early period (<6 weeks) to identify postoperative complications and their related surgical interventions, and a late period (>6 weeks) to identify subsequent surgical interventions for cosmetic reasons. Study parameters were: age at time of surgery, indication for MIDIIR, unilateral or (staged) bilateral mastectomy, previous lumpectomy, radiotherapy, size of the implant, early postoperative complications (within 6 weeks), and surgical interventions for cosmetic corrections (after 6 weeks).

Statistical Analysis

Data were analysed with the statistical program STATA version 7.0. Comparisons of percentages were made using the chi-square test. Continuous data were compared with the Mann-Whitney test. A P-value of <.05 was considered significant. The prognostic factors investigated in relation to complications occurring <6 weeks postoperatively were: age at MIDIIR (<45 vs ≥45 years), indication for MIDIIR (breast cancer vs prophylactic), previous lumpectomy (before mastectomy), size of the prosthesis and radiotherapy (only for recurrence after breast saving therapy).

RESULTS

Patient Characteristics (Table 1)

From January 1992 to August 2001, 356 patients underwent 510 MIDIIR. Bilateral MIDIIR was performed in 77 patients (154 MIDIIR: 140 MIDIIR were performed synchronously and 14 MIDIIR were performed metachronously). The median age at MIDIIR was 43 (range 26-66) years.

The indications for MIDIIR are given in Table 1. The majority of patients (n=239) were treated for breast cancer and had either modified radical mastectomy (MRM, n=207) or recurrent breast cancer after breast saving therapy (BST; n=32).

Prophylactic mastectomy followed by immediate reconstruction was performed in 241 asymptomatic women at high risk of breast cancer (159 BRCA 1, 23 BRCA 2 and 59 hereditary breast and ovarian cancer (HBOC). In 104 women there was no previous history of breast cancer, whereas 30 women were previously treated for (non-)invasive breast cancer. Thirty MIDIIR were carried out for miscellaneous reasons, including severe fibrocystic disease (3 patients, bilateral) and anxiety for contralateral breast cancer (especially in patients with lobular carcinoma or dense mammography) (n=24).

Of the 239 patients who underwent MIDIIR for breast cancer, 178 (74%) had a diagnostic lumpectomy before mastectomy. Of the 510 MIDIIR, a prosthesis of 150-200 ml was used in 16 cases, 220-300 ml in 64 cases, 350-400 ml in 222 cases, 420-500 ml in 203 cases and 600 ml was used in 5 cases.

Of the total 356 women, 39 received radiotherapy before or after MIDIIR: 32 patients were treated previously for breast cancer by BST involving radiation of the breast, and 7 patients received radiotherapy on the chest wall after mastectomy according to the guidelines in our institute after definitive pathological staging.

In 5 cases the patient urgently requested mastectomy without removal of the nipple (3 unilateral and 1 bilateral).

Table 1. Indications for MIDIIR from January 1992 to August 2001 in 356 patients undergoing 510 mastectomies

indication	total	unilateral	contralateral
BRCA1	159	87	72
BRCA2	23	12	11
HB(O)C*	59	38	21
Rec after BST**	32	15	17
Carcinoma	207	177	30
Miscellaneous	30	27	3
total	510	356	154

*hereditary breast ovarium cancer, **recurrence after breast saving therapy

Table 2. Early complications (<6 weeks) and late surgical interventions (>6 weeks) after 510 MIDIIR

Early	total	conservative	surgical
Infection	32	23	9
Necrosis	29	17	12
Bleeding	31	16	15
Prosthesis	20	-	13 removed 7 replaced
Late			
Scar/dog ear	45	-	45
Nipple	238	-	238
Prosthesis	83	-	20 removed 53 replaced 10 new

Complications within 6 Weeks (Table 2)

In the 356 women, 510 breast reconstructions were monitored for complications over a median follow-up period of 63 (range 3-116) months after MIDIIR. In 419 reconstructions (82%) no complications were observed whereas the remainder had one or more of the following complications: infection (32 cases), necrosis of the skin flap (29 cases), bleeding (31 cases) and protrusion of the prosthesis (20 cases) resulting in surgery in 9, 12, 15 and 20 cases, respectively. Thus within 6 weeks postoperatively, 56 MIDIIR (11%) underwent another surgical intervention. In 7 of the 20 MIDIIR with prosthesis-related surgery, the prosthesis was immediately replaced in 7 cases. This means an early loss of prosthesis of 13/510, i.e. 2.5%.

Late Surgical Interventions after 6 Weeks (Table 2)

Surgical interventions occurring more than 6 weeks postoperatively were needed in 366 MIDIIR. These were mainly related to cosmetic appearance, such as nipple reconstruction (238 of the 366 cases), change of prosthesis due to poor symmetry and correction of scar or dog ear. Of the 83 MIDIIR for which the indication was related to the prosthesis, in 20 cases the prosthesis was removed. The indications for this were infection and/or necrosis (6 cases), severe capsular formation (9 cases), whereas the request from 3 patients (2 bilateral) for definitive removal of the prosthesis (personal inconvenience) was not considered related to surgery. In 53 cases the prosthesis was replaced, because of poor cosmetic appearance and/or capsular formation, and in 10 cases a new prosthesis was placed after early removal.

During the entire follow-up period (3-116 months) complications related to surgery resulted in loss of prosthesis in 30 cases (6%). Secondary breast reconstruction was done in 15 cases; 5 by a new subpectoral, 5 by a subcutaneous prosthesis and 5 by a pedicled lattissimus dorsi flap in combination with a prosthesis. At the end of the follow-up period the overall loss of prosthesis was 18/510 (3.5%). Eighteen (5%) patients with a unilateral MIDIIR requested reduction mammoplasty on the opposite site.

Prognostic Factors related to Early Complications (Table 3)

The prognostic factors investigated in relation to complications occurring <6 weeks postoperatively were: age at MIDIIR (<45 vs ≥45 years), indication of MIDIIR (breast cancer vs prophylactic), previous lumpectomy (before mastectomy), size of the prosthesis and radiotherapy (only for recurrence after breast saving therapy). None of these prognostic factors were significant (P>.05 in all cases).

Table 3. Prognostic factors for early complications (<6 weeks)

	Prognostic factor	P-value
Age	< 45 years vs ≥ 45 years	0.53
Indication	Cancer vs Prophylaxis	0.64
Previous lumpectomy	Yes vs No	0.39
Size of the prosthesis	< 350 ml vs ≥350 ml	0.10
Previous radiotherapy	Yes vs No	0.50

DISCUSSION

In most cases mastectomy is performed using a transverse incision. However, when trying to reconstruct the breast the transverse scar gives considerable problems. First, the scar itself contracts and may have to be lengthened by (lateral) z-plasty. Second, usually there is an extension up to the median line which can never be corrected. Last but not least, there is a three-dimensional deficit caused by (too) ample resection and secondary contraction which requires placement of a tissue expander or use of myocutaneous flaps. Ideally, the center of the scar should give the most projection but unfortunately is contracted, sometimes showing dilated scar tissue. Finally, the transverse scar emphasizes the patch-like appearance of the abdominal skin contrasting with the thoracic skin.

In reduction mammoplasty some prefer the vertical scar[20-22], whereas others have tried to develop techniques with a short inframammary scar or a periareolar incision.[23-25]

The advantages of the MIDIIR technique are:

The upper dog ear gives a surplus in the region of the future nipple, providing more projection.[26] The lower dog ear is inverted after the suction drain is connected, thus creating a natural inframammary fold. Excising of the nipple causes some skin loss in the lower pole of the breast. This part is stretched by the correctly positioned prosthesis. In a few months a nicely rounded form appears. This confirms the investigation of van Egmond et al. who compared the inframammary scars of different types of mammary reductions concluding that it is the content that determines the final length of the inframammary scar.[27] Because the inner scar (pectoral muscle) and the outer scar (skin) cross each other, this is known as the envelope technique.

Apart from providing more stability to pressure (figure III), there are also advantages in perspective: cranially the woman can barely see the full lengh of the vertical scar. Frontally the scar appears much smaller because it follows the direction of the inframammary fold and lies on the shadow side of the breast. The actual length of the scar can be reduced by gathering the skin with a continuous intradermal suture. Although the appearance is usually very pleasing, all options remain open: e.g. the nipple can be reconstructed on the elevation of the upper dog ear, the silicone implant can be used as a spacer and can be replaced by (de-epithelised) flaps, and a contralateral reduction can be performed with an identical vertical inframammary scar, thus achieving more symmetry. Even if (for whatever reason) the implant has to be removed, the remaining vertical scar is less conspicuous and smaller than the usual horizontal one.

Since the introduction of DNA testing for the detection of BRCA1/2 mutation carriers, many women now consider a prophylactic mastectomy.[27] In an attempt to help these women in their free choice our group decided to offer them an immediate reconstruction after mastectomy.[29]

By 1992 we considered that we had accumulated sufficient experience with the surgical procedure described above, and the MIDIIR became a standard surgical tool in our hospital.

The aim of the present study was to investigate whether MIDIIR is acceptable with regard to complications and loss of prostheses. It is established that general factors such as obesity, previous radiotherapy and smoking can contribute to complications in reconstructive surgery,[30-33] whereas other factors such as type and size of the prosthesis, age, whether or not the indication is cancer, complete muscle coverage of the prosthesis, and inverted T-type of incision, are still disputed.[30,34,35] Therefore, the prognostic factors studied in our series were: age, implant size, previous lumpectomy in primary breast cancer, radiotherapy and type of indication. Although none of these factors proved to be significant, a comment is required concerning radiotherapy. An earlier study by our group reported radiotherapy to be a negative factor.[36] Reasons for this disparity compared with our present series may be improved patient selection, more experience in performing the surgical procedure, and the longer follow-up period in the present study.

The complication rate in the current series is 18%, which compares well with the 8-24% reported by others.[34,37-41] At the end of the follow-up period the prosthesis was definitively removed in 30 of the 510 cases (6%) compared with 1-16% reported in the literature.[30,33,35-39,42] In 15 of our cases a secondary reconstruction was performed.

For various reasons 18 (5%) patients with a unilateral MIDIIR requested mammoplasty of the opposite site. This percentage is very low compared with others reporting that 50% of their patients underwent reduction of the contralateral breast. [33,43] We have no explanation for this large difference.

In the present study no information was obtained about subjective factors such as cosmetic results and psychosocial satisfaction. (Fig 4) These will be investigated prospectively in our hospital; meanwhile the results of our pilot study on patient satisfaction have been published.[44]

Although we did not evaluate the costs of MIDIIR, it has been estimated that immediate reconstruction is less costly than delayed reconstruction because the latter requires additional hospitalisation and a more complex reconstructive procedures. It has been reported that the delayed reconstruction can cost $5100 and $10600 more than immediate reconstruction, irrespective of the type of reconstruction.[45,46]

In summary, our experience is that MIDIIR is a safe and quick procedure. MIDIIR in our hands had an acceptable complication rate and an acceptable rate of definitive loss of prostheses. The envelope technique allows placement of prosthesis up to 600 ml without the use of a tissue expander. With this technique another reconstruction can be made after removal of the silicone prosthesis. Regarding limitations, the MIDIIR is not the method of choice for obese patients and those with large breasts; to avoid a bad cosmetic result, in these latter cases another reconstructive technique (such as TRAM or LD flaps) is recommended. Additional studies are required to determine the long-term cosmetic results of MIDIIR, especially in women with increasing weight and patients with previous radiotherapy.

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CHAPTER IV.3

Clinical experience of prophylactic mastectomy followed by immediate breast reconstruction in women at hereditary risk of breast cancer (HB(O)C) or a proven BRCA1 and BRCA2 germ-line mutation. Management, morbidity and oncological aspects in 112 consecutive patients

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European Journal of Surgical Oncology 2002;28:627-632

ABSTRACT

Objective: Women with a proven BRCA1 or BRCA2 germ-line mutation or with a 50% risk of carrying the mutation, have an increased risk of breast cancer. Regular surveillance, chemoprevention or prophylactic mastectomy (PM) are options to detect breast cancer at an early stage or to reduce the risk. We describe the management of women who have opted for PM, the postoperative complications of PM, especially in combination with immediate breast reconstruction (IBR), and the oncological follow-up.

Methods: The medical records of all women who underwent a PM from December 1993 to December 1999 have been reviewed with respect to management, patient characteristics, complications and oncological follow-up.

Results: During the study period 112 women with a median age of 38.8 years opted for a PM: 76 were germline mutation carriers. After PM, 79 women without breast or ovarian cancer in their medical history, were free of disease after 2.5 years (median). Before PM, 29 women had been treated for breast cancer, 3.9 years (median) previously; 5 of these women had developed metastatic disease by the last consultation. Before PM, 2 patients had been treated for DCIS and 2 patients for ovarian cancer. Four DCIS were found; none of these women had evidence of disease 4.0 years (median) after PM. In 59 women laparoscopic prophylactic bilateral oophorectomy (PBO) was performed; 36 simultaneously with PM and 23 separately. A total of 103 women (92%) opted for IBR. After PM, the complication rate for IBR was 21%: 11% within 6 weeks and 10% at long-term follow-up (median 3,5 years) after PM, including the removal of 10 prostheses.

Conclusions: Women with an increased risk of breast cancer due to a genetic predisposition should be adequately informed about the different treatment options in the setting of a multidisciplinary approach. PM can simultaneously be combined with PBO and IBR. IBR can facilitate the decision to undergo a PM. PM followed by IBR has an acceptable complication rate.

INTRODUCTION

Advances associated with genetic testing have allowed to identify women at increased risk of breast cancer. These women are members of a hereditary breast (and ovarian) cancer (HB(O)C) family or carry a mutation in either the BRCA1 or BRCA2 gene. The estimated lifetime risk of breast cancer in carriers of these germ-line mutations, ranges from 55-80%.[1,2] If genetic testing in a family is inconclusive, the risk of breast cancer for a 50% risk carrier ranges from 30-50%. Characteristics of hereditary breast cancer are: a young age at onset, frequently bilateral occurrence, and an incidence of breast cancer in multiple generations.[3,4] Although BRCA-associated breast cancers present with adverse clinical and histopathologic features, the prognosis appears to be similar to that of sporadic breast cancer.[5] Regular surveillance, chemoprevention or prophylactic bilateral mastectomy are options that are discussed with women at increased risk of breast cancer. None of these options, however, completely protects against breast cancer. Intensive surveillance aims to detect breast cancer at an earlier stage. The real value of chemoprevention is still under investigation. Cases of breast cancer after bilateral (subcutaneous) mastectomy have been documented, demonstrating that residual mammary tissue is left behind.[6,7]

Since the clinical introduction of DNA-testing for the determination of a BRCA1/2 gene mutation and the start of the Family Cancer Clinic at The Daniel den Hoed Cancer Centre in 1991, many women have considered a prophylactic mastectomy (PM).[8] This article describes the management of the first 112 women who have chosen for PM. Furthermore, the postoperative complications of PM, and the preliminary results on oncological follow-up after PM are reported. Special attention is paid to the immediate breast reconstruction (IBR) by subpectorally placed silicone prosthesis after PM.

PATIENTS AND METHODS

Routing of Patients

Women with an increased risk of breast cancer due to a genetic predisposition are seen at our Family Cancer Clinic. This group consists of either BRCA1 or BRCA2 gene mutation carriers, or 50% risk carriers. These are defined as a daughter of an affected woman from an HB(O)C family. At the Family Cancer Clinic women are extensively informed about their risk of breast cancer, the screening schedule, intensive surveillance and the possibility of PM. The policy at the Family Cancer Clinic of the Daniel den Hoed Cancer Centre is to inform these women about both options: regular intensive surveillance or prophylactic surgery.

The patients are referred to one of the two surgical oncologists involved in the Family Cancer Clinic, and if a patient considers an IBR, an appointment is made with our plastic surgeon. Our gynaecologist assesses the risk of ovarian cancer and the option of regular screening (i.e. yearly

pelvic examination, transvaginal ultrasound and tumour marker) or prophylactic bilateral oophorectomy (PBO). If a woman chooses for PBO, this can be combined in one session with PM.

If women decide to undergo prophylactic surgery, on their own initiative they make another appointment at the surgical outpatient clinic to discuss remaining questions and to arrange the date of surgery.

Surgical Technique

The surgical oncologist and the plastic surgeon perform the PM and IBR as a team. The operation is performed under general anaesthesia with the patient in a half supine position. The mastectomy is done through a vertical, peri-areolar incision, which extends from just above the nipple down to the submammary fold. The breast including the superficial or subdermal fascia (creating thin skin flaps), the axillary tail, the nipple-areolar complex, and the fascia of the pectoral muscle are removed. The axillary nodes are not dissected. In case of IBR, the silicone prosthesis is inserted in a pocket created below the pectoral muscles with some extension to the space underneath the rectus abdominis and the serratus. In case of unilateral PM the incision matches the initial incision used for the previous contralateral radical mastectomy. Two vacuum drains are left behind and removed when the production is 0 cc during 24 hours, or less than 20 cc during 2 consecutive days.

A nipple reconstruction (by tattooing or flap reconstruction) may be performed 6 to 12 months after PM, when the reconstruction has its definite shape.

Data Collection

The medical records of all women who underwent a PM from December 1993 to December 1999 have been reviewed. The following data were collected: age, medical history, indication for PM, pathological results, postoperative complications (short and long term) and oncological follow-up.

Statistical Analysis

Pearson's chi-squared test and Fisher's exact test are used to test for differences in proportions between subgroups. Significance is attributed to $P<0.05$.

RESULTS

Patient Population

From December 1993 to December 1999, 112 consecutive women underwent a prophylactic mastectomy (PM). The median age at the time of PM was 38.8 years (range 23.4 – 63.9 years). The median follow-up after PM was 2.8 years (range 1.0 – 7.0 years).

Table 1. TNM classification and treatment of previous breast cancer in women undergoing prophylactic mastectomy

TNM	N	BCT	MRM	MRM + IBR
T1N0M0	17	11	2	4
T2N0M0	9	3	4	2
T1N1M0	1	1	-	-
T2N1M0	1	-	1	-
T3N1M0	1	-	1	-
Total	29	15	8	6

BCT = breast conserving therapy
MRM = modified radical mastectomy
IBR = immediate breast reconstruction
Values are numbers of patients

Germ-line mutations were present in 76 women, consisting of 63 BRCA1 and 13 BRCA2 mutations. Thirty-six women belonged to a HB(O)C family and were defined as 50% risk carriers (daughters of affected women). Fig 1 shows that in our institution during the last 5 years PM has mainly been performed in women with an identified germ-line mutation rather than 50% risk carriers.

In 112 women, 207 PMs were performed: 95 bilateral mastectomies (BPM) and 17 unilateral mastectomies (UPM). The contralateral breast of the women undergoing a UPM had previously been removed in 14 patients. The amputation had been followed by IBR in 5, by secondary reconstruction in 7, and amputated without reconstruction in 2 women. The remaining 3 women who underwent UPM had previously been treated by breast conserving therapy (BCT) of the contralateral breast.

In 79 women there was no previous history of breast cancer, whereas 29 women had previously been treated for invasive breast cancer, 2 women for DCIS and 2 women for ovarian carcinoma. Of the 29 women with a history of invasive breast cancer, 15 had been treated by BCT and 14 by modified radical mastectomy (MRM); in the latter group 6 women had IBR with a subpectorally placed silicone prosthesis. The median interval between primary breast cancer surgery and additional PM was 3.9 years (range 5 months – 16.1 years). The classification of these infiltrating breast cancers is given in Table I (UICC TNM classification of breast cancer). The surgical therapy of DCIS in 2 women had consisted of single lumpectomy and mastectomy, 5 months and 2.1 years, respectively, before PM. In this population 2 women had been treated for ovarian cancer 1.2 and 4.8 years, respectively, prior to PM; both these women were BRCA1 mutation carriers.

Of all women undergoing a PM, 103 had IBR by a subpectorally placed silicone prosthesis, and 9 women had no a reconstruction of the breast after PM. Of these 103 women, 65 had nipple reconstruction by tattooing or local flap reconstruction after IBR.

Table 2. Complications after prophylactic mastectomy followed by immediate breast reconstruction with a subpectorally placed silicone prosthesis

Complication	Early complication < 6 weeks after operation		Late complication > 6 weeks after operation	
	N (%)	Surgery	N (%)	Surgery
Bleeding	10 (5.2)	10	-	-
Infection	5 (2.5)	3	4 (2)	4
Wound necrosis	2 (1)	2	1 (0.5)	1
Pneumothorax	2 (1)	-	-	-
Luxation	2 (1)	2	4 (2.5)	4
Capsular contracture	-		14 (7.2)	8
Total	21 (11)	17 (8)	23 (12)	17 (9)

Values are number of patients (percentage)

Laparoscopic prophylactic bilateral oophorectomy was performed in 59 women (53%), 36 simultaneously with PM and 23 consecutively: 46 women were BRCA1 and 9 women were BRCA2 gene mutation carriers, while 4 women were 50% risk carriers.

Histopathologic Examination

At pathologic examination no DCIS or invasive breast cancer was found in 108 women (97%). In 4 women unilateral DCIS was found; 3 of these women had a previous history of invasive breast cancer in the contralateral breast 7.3 years, 7.1 years and 5 months, respectively, before PM. Two women were screened preoperatively by mammography and ultrasound of the breast, which were classified as benign in both patients.

Ovarian cancer was not found in any of the women undergoing PBO.

Follow-Up

I. Complications

Nine patients underwent PM without immediate reconstruction: 5 bilateral and 4 unilateral (contralateral mastectomy for breast cancer (3) or DCIS (1) in medical history). Two patients had a postoperative haemorrhage, requiring surgical intervention.

Of the 103 patients who underwent PM with IBR, 73 patients (71%) had no complication during follow-up. A total of 103 patients underwent 193 PMs with IBR: 90 bilateral and 13 unilateral. The median follow-up after IBR was 3.5 years (range 1– 7.0 years). In 163 IBRs (82%) no complications were observed. Table 2 presents the early and late complications of PM followed by IBR. Within 6 weeks after operation 21 complications (11%) were seen, requiring surgical re-intervention in 18 cases. The most common postoperative complication was bleeding (n=10). Capsular contracture was the most common late complication. Over the entire follow-up period 10 prostheses were removed (5%); 7 due to infection, 2 due to wound necrosis, and 1 due to pain. Five secondary breast reconstructions were done after loss of

Table 3. Relation between radiation therapy and complications

Radiotherapy	N	Early complication		Late complication		Loss of prosthesis	
Total	193	21		23		10	
Yes	14	6	43%	6	43%	4	29%
No	179	15	8.4%	17	9.5%	6	3.4%
P		0.001		0.002		0.002	

the prosthesis: 3 with single use of prosthesis, and 2 in combination with a latissimus dorsi flap. Thirteen reconstructions (6.7%) needed cosmetic corrections, i.e. correction of dog-ears, protrusion or augmentation.

Of the 17 patients who had been treated in medical history by BCT for invasive breast cancer (n=16) and for DCIS (1), 14 underwent an ipsilateral PM. Fourteen breast reconstructions were done in the irradiated area. Table 3 presents the relation between radiotherapy and complications. The incidence of early (43%) and late complications (43%) was significantly higher in the group women who received radiation therapy in the past, compared to those without radiation (8.4% early and 9.5% late complication rate; P=0.001 and 0.002, respectively). Loss of prosthesis occurred significantly more often in prostheses that were implanted following radiation therapy (P=0.002).

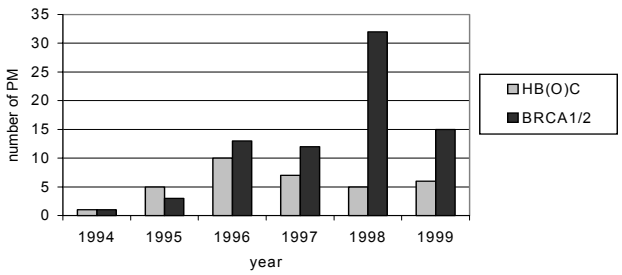

Figure 1. Number of PM each year, in 50% risk carriers from HB(O)C families and in BRCA1/BRCA2 germ-line mutation carriers, in the present study population (n=112)

II. Oncologic Follow-Up

At the last consultation, 24 of the 29 women with a previous history of breast cancer were alive without evidence of disease with a median follow-up of 7.7 years after primary breast cancer diagnosis (range 3.9 – 18.8 years). Five women were alive with visceral metastatic disease, which was diagnosed 2.6, 3.4, 3.9, 4.0, and 5.7 years, respectively, after PM. These 5 women were treated 0.9, 5.4, 0.6, 0.4 and 2.7 years, respectively, before PM for stage T1N0M0 in 3, and T2N0M0 in 2 women.

All 4 women with DCIS found at pathologic examination of PM were alive without evidence of disease with a median follow-up of 4.0 years (range 2.0 – 4.6 years) after PM.

The 79 patients who had no previous history of breast cancer, ovarian cancer or DCIS, and with a negative pathologic examination of PM, remained free of disease after a median follow-up of 2.5 years (range 1 – 5.9 years) after PM.

DISCUSSION

Prophylactic surgery in women at increased risk of breast cancer remains a controversial procedure.[9,10,11] Until recently, only two published studies have used statistical models to predict the benefit of prophylactic mastectomy in high-risk women[12] or in mutation carriers[13]; they model a 90% and an 85% reduction in risk of breast cancers, respectively. Although these results are very optimistic about the efficacy of PM, caution should be applied whilst awaiting the results of prospective studies focusing on the different treatment strategies in high-risk women.

Over the last five years, in our institution PM has mainly been performed in women with an identified germ-line mutation rather than in 50% risk carriers. Carrying a BRCA1/2 germ-line mutation means a 55-80% lifetime risk to develop breast cancer, while 50% risk carriers from a HB(O)C family have a lifetime risk of 30-45%. PM is discussed in case of a demonstrated gene mutation or an estimated more than 30% lifetime risk of developing breast cancer.[14] Hartmann et al. report a reduction of about 90% in the incidence of invasive breast cancer after PM in highrisk women at a median follow-up of 14 years.[12] Meijers-Heijboer et al. recently published a prospective study on 139 women with a proven BRCA1 or BRCA2 mutation. Half of the women underwent PM and the others chose for regular surveillance. After a median follow-up of 2.2 years, no breast cancer was observed after PM, while under regular surveillance 8 incident breast cancers were diagnosed. Although in this latter study the follow-up is short and the number of patients is limited, it is concluded that PM in proven mutation carriers strongly reduces the incidence of breast cancer.[15]

The efficacy of PM depends on the ability to remove all breast tissue. In high-risk patients the development of cancer in the residual breast tissue following mastectomy is reported to range from 1-9 %.[16,17] The only data on breast cancer after PM are reported in patients undergoing a subcutaneous mastectomy, which does not include removal of the nipple-areolar complex.[12,18,19] To minimise the amount of residual breast tissue after PM, the PM procedure as performed in the present study is recommended, i.e. removal of all breast tissue including the superficial or subdermal fascia, the axillary tail, the nipple-areolar complex and the pectoral fascia. In our study no breast cancer has developed after PM, but the follow-up is short.

In the present study 29 women were previously treated for invasive breast cancer and 3 for DCIS. It is thought that the prognosis for women with BRCA-1 or BRCA-2 associated breast cancer is worse than for women with sporadic cancer. Recent studies, however, do not report differences in disease-free and overall-survival between these two groups.[3,4,20,21] The incidence

of early local recurrence after BCT in women with a positive family history appears to be the same as that in women with BRC-associated breast cancer.[22] On the other hand Turner et al. found an elevated frequency of ipsilateral breast tumour recurrence after BCT with a median interval of 7.8 years. They suggest that, based on the relatively long disease free interval and the histological and clinical criteria, these local recurrences in fact represent a new primary breast cancer.[23] Therefore, an ipsilateral PM after BCT may be an option on the bases of the increased risk in high-risk women to reduce the risk of developing a local recurrence or a second primary tumour.

Moreover, women with BRCA-associated breast cancer have an increased risk for contralateral breast cancer compared with women with sporadic breast cancer, which is also dependent on the age at onset of the primary breast cancer.[3,5,24] Therefore, it is understandable that mutation carriers with breast cancer request a contralateral mastectomy. In the present study, 29 women have a history of breast cancer; in 3 of these women (10.3%) after PM DCIS is found at pathological examination of the contralateral breast. Seventy-eight women do not have breast cancer or DCIS in medical history; 1 of this group (1.3%) had DCIS at pathological examination.

Women with BRCA1 and BRCA2 mutation are believed to have a 15-60% risk of developing ovarian carcinoma during lifetime.[1,2] These women may consider a prophylactic oophorectomy. In the present study 75% of the women with BRCA1 and 69% of the women with BRCA2 underwent a prophylactic laparoscopic oophorectomy. Both surgical procedures can be combined, a topic which will be explored in a future study. To avoid postmenopausal complaints unaffected women may receive hormonal substitution.[25]

We believe that the decision for PM becomes easier if the women are offered the possibility of IBR. In our study population, most women (94%) have chosen for IBR after PM. However, IBR with a subpectoral placed silicone prosthesis is not without complications. In the present study IBR has an overall complication rate of 21% (11% early and 10% long-term complication rate). The main early complication is bleeding in 10 IBRs, all leading to surgical intervention; this is in contrast to findings in a previous study on the morbidity of IBR.[26] A possible explanation for this high occurrence is that our indication for re-intervention is strict; i.e. less haematoma around the prosthesis is accepted in order to prevent infection. On the other hand, 71% of all IBRs are without complications, which is an acceptable percentage. Problems of IBR with a silicone prosthesis after BCT in combination with radiation therapy have been reported. Complications, especially capsular contracture and loss of prosthesis are more common in prostheses inserted after irradiation.[26] This is in accordance with the results of the present study, in which complications and loss of prosthesis is significantly higher in IBR in women with a history of radiation therapy of the breast.

Another problem of IBR is the relatively high number of surgical re-interventions needed to optimise cosmetic aspects, especially scar and symmetry correction. In the present study only 6.7% of the IBRs needed secondary intervention for cosmetic reasons. In the Daniel the Hoed Cancer Centre the use of the so-called inverted drip (vertical) incision is introduced to minimise

the length of the scar and to optimise the cosmetic result by creating a small scar at the inferior part of the breast. As mentioned above, PM includes resection of the nipple-areolar complex. For cosmetic reasons it is better to perform the nipple-reconstruction 6 to 12 months after the PM, when the reconstructed breast has its definite shape. More than half of the patients in this study had a nipple-reconstruction.

CONCLUSIONS

The ultimate goal of all clinicians working in the outpatient clinic is to inform women at high risk for breast cancer as thoroughly as possible in the setting of a multidisciplinary approach. All women are scheduled for intensive surveillance and the information on PM and IBR is given on request. The women make the final decision for PM themselves. The indication for PM has shifted to proven germ-line mutations rather than for HB(O)C. PM can be done simultaneously with BPO. Based on our patient group, we have the impression that IBR can facilitate the definitive decision to undergo PM. Complications after IBR with a subpectoral silicone prosthesis occur significantly more often in previously irradiated patients. PM followed by IBR in non-irradiated patients has an acceptable complication rate.

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CHAPTER IV.4

Locoregional recurrence after skin-sparing mastectomy followed by immediate breast reconstruction with a subpectorally placed silicone prosthesis

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Submitted for publication

ABSTRACT

Objective: To examine the incidence of locoregional recurrence (LRR) and associated risk factors in a population of women who underwent skin-sparing mastectomy (SSM) and immediate breast reconstruction (IBR) with a subpectorally placed silicone prosthesis.

Methods: A consecutive series of 88 patients (92 breast cancers) with invasive carcinoma underwent SSM and IBR with a subpectorally placed silicone prosthesis (June 1991 to October 1997). Data were collected from the medical records of all women and a histopathologist reviewed all pathological results.

Results: Mean patient age was 43 years (34% were ≤ 40 years). The AJCC staging was I=41%, IIa=32%, IIb=15%, IIIa=2% and 10% unknown. Thirty-two percent of the tumours were multifocal carcinomas and 24% had multifocal carcinoma in situ next to the primary tumour. The median number of axillary nodes removed was 13. When axillary dissection was done through the vertical peri-areolar incision significant less lymph nodes were removed and significantly more inadequate dissections were done (P=0.004 and P=0.001, respectively).

With a median follow-up of 6.1 years, 14 LRR (15%) were seen: 10 chest wall recurrences and 4 axillary recurrences, median 3.7 years after SSM. Multifocal carcinoma (P=0.03) and multifocal carcinoma in situ next to the primary tumour (P=0.04) were associated with a higher CR rate. LRR was associated with distant metastases (P=0.006) and with a trend towards decreased overall survival (P=0.07).

Conclusion: Multifocal carcinoma and multifocal carcinoma in situ are significant negative prognostic factors for chest wall recurrence after SSM for invasive breast cancer. Axillary dissection should be done through a separate axillary incision instead of the vertical peri-areolar incision.

INTRODUCTION

Chest wall recurrence (CR) of breast cancer after mastectomy usually presents as one or more asymptomatic nodules located in or near the scar of the mastectomy or skin flaps. Approximately 80 to 90% of CRs appear within 5 years following mastectomy; nearly all occur within 10 years.[1] Although CRs up to 50 years after initial therapy, many of these may in fact be new primary tumours, rather than "recurrences". The rate of CR after 10-year follow-up is 12%.[3,4] Axillary recurrence (AR) usually appears as an asymptomatic mass in the axilla. The cumulative risk of AR after full axillary clearance or dissection of the lower and middle parts of the axilla (level I and II) ranges from 0.5 to 3.0%.[5-10] It has been shown that larger tumour size, negative estrogen receptor protein status, vascular invasion, increasing numbers of involved lymph nodes, and decreasing number of lymph nodes examined are significant factors for increasing the rate of locoregional recurrence (LRR) with or without simultaneous distant failure.[4,11]

The relationship between LRR of breast cancer and subsequent metastasis and survival is controversial. Some patients with isolated locoregional disease may have slowly disseminating disease; effective local therapy may cure these patients.[12-14] Other patients have aggressive disease, giving rise to early and clinically overt distant metastases; in these patients the diagnosis of LRR may be a marker of poor prognosis.[15] It is presently unknown whether LRR is a source of distant metastases or simply a marker of dissemination.[16-19]

Skin-sparing mastectomy (SSM), i.e. removal of breast tissue and nipple-areola complex, followed by immediate breast reconstruction (IBR) has become a standard of care for women with breast cancer who need or choose a mastectomy. It has been advocated as an oncologically safe technique for the management of patients with early-stage breast cancer.[20-24] Preservation of the inframammary fold and native skin enhances the aesthetic result of breast reconstruction. A limited number of studies have reported an acceptable CR rate of 3-7% after SSM with a mean follow-up of 44 months.[20-24]

In 1990, SSM followed by IBR with a subpectorally positioned silicone prosthesis was introduced in the Daniel den Hoed Cancer Centre. This is the simplest method for breast reconstruction and does not mask the development of CRs in skin, subcutaneous tissue or chest wall musculature. In this article we examine the incidence of LRR and factors associated with it in a population of women who underwent SSM and IBR with a subpectorally placed silicone prosthesis.

PATIENTS AND METHODS

Data Collection

The medical records of all women who underwent SSM for invasive breast cancer followed by IBR with a subpectorally placed silicone prosthesis from June 1991 to October 1997 have been

reviewed. The following data were collected: medical history, preoperative clinical examination, age at operation, surgical technique, pathological results, oncological adjuvant therapy, and oncological follow-up (i.e. incidence of locoregional recurrence, disseminated disease, and death). A histopathologist reviewed all pathological results.

Surgical Technique

The surgical oncologist and the plastic surgeon perform the SSM and IBR as a team in a 1.5-hour session. The operation is performed under general anaesthesia with the patient in a half supine position. The SSM is done through a vertical, peri-areolar incision, which extends from just above the nipple down to the inframammary fold. The breast including the superficial or subdermal fascia (creating thin skin flaps), the axillary tail, the nipple-areolar complex, and the fascia of the pectoral muscle, are removed. The axillary nodes are removed en bloc through the same vertical incision or separately through a secondary axillary incision. The borders of the axillary dissection are the latissimus dorsi muscle (dorsal), the thoracic wall below the major and minor pectoral muscles (ventral), and the lower border of the axillary vein (cranial). After the mastectomy the plastic surgeon inserts the silicone prosthesis (Laboratoires Eurosilicone, Apt, France) in a pocket created below the pectoral muscles with some extension to the space underneath the rectus abdominis and the serratus. Two vacuum drains are left behind, one subcutaneous and one subpectoral, and are removed when the production was 0 cc during 24 hours, or less than 20 cc during 2 consecutive days. A third vacuum drain is axillary situated and removed when the production is less than 50 cc during 24 hours.

Pathological Revision

Pathological slides of the women with SSM have been reviewed by one histopathologist (M.K.), except for 5 cases in which they were not available; in these latter cases the original reports were used. Special attention was paid to tumour extension, type of carcinoma, Bloom and Richardson (BR) classification and mitotic activity index (MAI), multifocality, angio-invasion and perineural tumour growth. In case of the presence of a carcinoma in situ (CIS) component next to the invasive breast cancer, type, grade, extensity and multifocality of CIS were examined. The removed axillary lymph nodes were recounted and scored for extracapsular extension of tumour growth and tumour involvement of the apical lymph node of the axilla.

The following definitions are used. In case of multiple simultaneous ipsilateral carcinomas, i.e. multifocality, the diameter of the largest carcinoma is used to classify T. The histological grade and MAI of the tumours are scored according to the Elston modification of the Bloom and Richardson system.[25] Vascular invasion is considered to be present if distinct tumour emboli are seen in more than 3 endothelium-lined vessels, including both blood and lymphatic vessels. Perineural growth is defined as infiltration of tumour cells in the perineurinum and not merely the presence of nerve branches in the tumour mass.

Estrogen receptor (ER) and progesterone receptor (PR) status is measured biochemically.

Ductal carcinoma in situ (DCIS) was characterised by proliferation of malignant breast epithelial cells, which are confined to the ductal system, and do not invade the surrounding non-specialised stroma. Lobular carcinoma in situ (LCIS) is characterised by distended acini with a uniform population of malignant cells and with expansion of at least half of the acini in the lobular unit. Both DCIS and LCIS are pre-invasive forms of breast cancer.

Extensive carcinoma in situ (ECIS) is defined as more than 25% CIS of the tumour mass with extension beyond the main tumour border.

At least 10 axillary nodes need to be removed to avoid misclassification and to optimise local control in the axilla.[26-29] Therefore we define an axillary dissection inadequate when less than 10 lymph nodes are removed.

The American Joint Committee on Cancer (AJCC) system is used for the pathologic staging system and is based on the TNM system, in which T referred to tumour, N to nodes, and M to metastasis.[30] CR is defined as reappearance of cancer in the ipsilateral chest wall, or skin overlying the chest wall after initial therapy. Axillary recurrence (AR) is defined as reappearance of tumour involving the ipsilateral axillary lymph nodes.

Statistical Analyses

Endpoints included chest wall recurrence (CR), locoregional recurrence (LRR) and overall survival (OS). CR and LRR are calculated from mastectomy until reappearance of tumour and determined for all 92 SSM. Patients without LRR are censored at the date of last consultation. OS is calculated from mastectomy until death from any cause and was determined for the first operation in each of the 88 patients. Patients still alive at the date of last contact are then censored. CR, LLR and OS are estimated by the Kaplan-Meier method. The following variables are included in the analysis of prognostic factors for CR: age (continuous as well as ≤ 40 versus >40 years), tumour location (central versus outer quadrant), axillary dissection (vertical versus separate incision), T classification, Bloom Richardson classification, multifocality (multifocal carcinoma and multifocal CIS), extensive CIS, angio-invasion, MAI, ER and PR and nodal status. Perineural growth is not included in the analysis as this is present in only 4 patients. Univariate Cox regression analysis is used to determine differences between subgroups. Moreover, LRR is included as a time- dependent covariant to see whether occurrence of LRR increased the risk of subsequent distant metastasis or predicted for decreased overall survival. The hazard ratio (HR) and corresponding 95% confidence intervals (CI) and P-values are calculated. All P-values are two-sided and a significance level $\alpha = 0.05$ is used.

RESULTS

Patients

Between June 1991 and October 1997, 88 women underwent SSM for invasive breast cancer followed by IBR. Four patients developed contralateral breast cancer during the study period and were treated by SSM and IBR, resulting in 92 SSMs followed by IBR. The median age at time of operation was 45 years (mean 43 years; range 26-59 years). Thirty women (34%) were age ≤ 40 years at time of operation.

By clinical examination the localisation of the tumour was in the following quadrants: 36 lateral-cranial, 1 lateral-caudal, 10 medial-cranial, 2 medial-caudal, 36 central, and 2 had overlapping localisation. In 5 women tumour localisation was unknown.

Surgical Technique

A diagnostic lumpectomy was done in 54 women before definite surgery. Excision of the tumour biopsy scar during mastectomy was performed in 37 women; the other 17 women did not have resection of the biopsy scar. The axillary dissection was performed by the vertical incision as described above in 60 women. In 30 women axillary dissection was done through a separate incision in the axilla. In 2 women the axillary dissection was not performed, because of a minimal invasive tumour component (i.e. less than 5 mm) found by coincidence at pathological examination next to carcinoma in situ, which was the indication for the amputation.

Pathological Features (Tables 1, 2)

The most common form of breast cancer in this population was ductal carcinoma (n = 70) followed by lobular carcinoma (n=22). The mean tumour diameter was 2.1 cm (median 1.8 cm; range 0.1-8.0 cm). Most tumours (66%) were ≤ 2 cm in diameter (T1a-c). Table 1 gives the Bloom Richardson (BR) classification; in 8 cases no BR classification or MAI could be given due to lack of the possibility to revise pathological samples (n=5) and the very small tumour diameter (n=3). The receptor status was known of 60 tumours (65%) and was mostly positive for ER (40%) and PR (51%). Multifocality of carcinoma was seen in 29 specimens (32%). In 75 mastectomy specimens (82%) CIS was found next to the primary tumour. The majority of carcinoma in situ was DCIS (81%). In 30% the in situ carcinoma (CIS) component was multifocal and in 40% it was extensive CIS.

Metastatic spread to axillary nodes was seen by pathological examination of the specimens in 28 women (33%). In 18 axillary dissections there was extracapsular tumour growth and in 12 there was nodal involvement in the apical lymph node. The pathological staging and TNM classification are given in Table 2; most women had stage I breast cancer (41%).

Axillary Lymph Nodes

On pathological examination of the specimens no lymph nodes were found in 6 women (5 vertical incision; 1 separate incision). The median number of axillary nodes removed by dissection

Table 1. Tumour characteristics

Total		92 (100%)
Type of carcinoma		
	ductal	70 (76%)
	lobular	22 (24%)
T stage		
	1	61 (66%)
	2	23 (25%)
	3	6 (7%)
	unknown	2 (2%)
N stage		
	0	56 (61%)
	1	28 (30%)
	unknown	8 (9%)
BR Classification		
	I	21 (23%)
	II	41 (45%)
	III	22 (24%)
	unknown	8 (9%)
MAI		
	≤ 5	50 (54%)
	6-10	16 (19%)
	> 10	18 (22%)
	unknown	8 (9%)
Estrogen receptor		
	positive	37 (40%)
	negative	23 (25%)
	unknown	32 (35%)
Progesterone receptor		
	positive	47 (51%)
	negative	13 (14%)
	unknown	32 (35%)
Multifocal carcinoma		
	yes	29 (32%)
	no	63 (68%)
Multifocal carcinoma in situ		
	yes	22 (24%)
	no	70 (76%)
Vascular invasion		
	yes	24 (28%)
	no	62 (67%)
	unknown	6 (7%)

Table 2 . Staging and TNM-classification

Total		92 (100%)
I		38 (41%)
	T1aN0M0	4
	T1bN0M0	9
	T1cN0M0	25
IIa		29 (32%)
	T1aN1M0	1
	T1bN1M0	3
	T1cN1M0	12
	T2N0M0	13
IIb		14 (15%)
	T2N1M0	10
	T3N0M0	4
IIIa		2 (2%)
	T3N1M0	2
Unknown		9 (10%)

was 13 (mean 13; range 0-36 nodes). When the axillary dissection was done by vertical incision 11 nodes (median) were removed, compared to 14 nodes (median) when axillary dissection was done through a separate axillary incision (P= 0.004). Moreover inadequate axillary dissection was done in 26 women through a vertical incision compared to 3 inadequate dissections by a separate axillary incision (P=0.001).

Adjuvant Oncological Therapy

Fifty-seven women (62%) were treated by surgery only. Thirty-two women (35%) received adjuvant systemic therapy, 24 chemotherapy, 6 endocrine therapy and 2 a combination of both systemic therapies. All 28 node-positive women received systemic therapy. Three women had no positive lymph nodes and received chemotherapy due to a bad tumour differentiation.

Fifteen women received locoregional radiation therapy of the chest wall and axilla, because of a combination of extracapsular extension of tumour growth or tumour involvement in the apical lymph node of the axilla (12). The chest wall was radiated in 3 women extraprotocollair.

Oncological Follow-Up

At the last consultation 73 women (83%) were still alive (mean) 6.1 years (median 6.1; range 3.0-9.6 years) after SSM and IBR. Sixty-one women (84%) had no evidence of disease and 12 (16%) were alive but had visceral metastatic disease. Fifteen women (17%) died median 4.8 years (range 0.6-7.9 years) after SSM and IBR; one due to metastatic liposarcoma without evidence of metastatic breast cancer and the other 14 due to metastatic breast cancer. The 5-year overall survival after SSM and IBR was 89%. The probability of developing metastasis within 5-years after operation was 29%.

Table 3. Univariate Cox regression of chest wall recurrence (CR)

Factor		n	% LR	HR	95% CI	P-value
age						.21
	≤ 40 years	31	15	1		
	> 40 years	61	9	0.46	0.13-1.58	
T						.92
	1	61	11	1		
	2	23	13	1.07	0.28-4.14	
	3	6	-	-		
N						.54
	0	56	14	1		
	1	28	4	0.61	0.13-2.95	
Bloom Richardson						.25
	I	21	11	1		
	II	41	13	0.80	0.13-4.79	
	III	22	26	2.55	0.49-13.2	
MAI						.31
	≤ 5	50	9	1		
	6-10	16	8	0.64	0.07-5.45	
	> 10	18	25	2.47	0.66-9.25	
multifocal carcinoma						.03
	no	63	6	1		
	yes	29	23	4.02	1.13-14.3	
multifocal CIS						.04
	no	70	6	1		
	yes	22	26	3.58	1.03-12.4	
extensive CIS						.31
	no	50	9	1		
	yes	37	15	1.94	0.55-6.88	
vascular invasion						.34
	no	62	11	1		
	yes	24	16	1.84	0.52-6.54	
estrogen receptor						.87
	no	23	11	1		
	yes	37	11	1.15	0.21-6.28	

N = number of patients
HR = hazard ratio
95% CI = 95% confidence interval
%LR = actuarial 5-year probability of CR

Over the period under review 14 cases of LRR were observed, median 3.7 years (range 0.6-6.3 years) after SSM and IBR. Ten recurrences were detected in the native skin flaps and 4 in the ipsilateral axilla. The 5-year probability of chest wall recurrences was 11%, and was 15% of LRR.

Prognostic Factors and Locoregional Recurrence

1. Local recurrence

   Table 3 gives the significant risk factors for CR. Multifocal carcinoma (P=0.03) or the presence of multifocal carcinoma in situ next to the primary tumour (P=0.04) were the only significant risk factors for the development of chest wall recurrence. The hazard ratios of histologic multifocality and multifocal CIS are 4.0 (95% CI=1.1-14.3) and 3.6 (95% CI=1.0-12.4), respectively. CR was not significantly associated with age, tumour size, nodal status, BR classification, MAI, estrogen receptor protein status and extensive DCIS.

2. Axillary recurrence

   The 4 ARs occurred in 3 women with N0 and in 1 woman who had not received an axillary dissection. AR occurred twice in an inadequate dissection (i.e. less than 10 nodes removed) and once after removal of 10 lymph nodes.

3. Locoregional recurrence and prognosis

   The median length of follow-up after diagnosis of LRR was 2.0 years for the total group and 2.1 years for the patients who are still alive. Five patients with LRR are still alive without distant metastases 1.5 years (median) after diagnosis of LRR. Eight women with LRRs developed distant metastasis, 5 after discovery of the LRR, 2 simultaneously, and 1 before the appearance of LRR. Of these 8 patients with LRR and distant metastasis, 4 died and 4 patients are still alive with evidence of disease.

   Univariate Cox regression analysis with LRR as time-dependent covariate showed that LRR was associated with distant metastasis (HR=4.3, 95% CI=1.5 – 12.2, P=0.006), and there was a trend towards decreased overall survival (HR=3.0, 95% CI=0.9 – 10.0, P=0.07).

DISCUSSION

Locoregional recurrence (LRR) after mastectomy is an important problem for several reasons. LRR may be difficult to control and cause substantial morbidity.[4] In addition, such failures may also reduce patients' chance of cure. Almost all patients with LRR eventually develop distant metastases and die of metastatic breast cancer.

The objective of this study was to demonstrate that planning SSM and IBR, application of an oncologically safe technique results in an identical LRR rate to that observed after regular mastectomy without breast reconstruction. The LRR rate after SSM with IBR in this study was

15%; 11% CR and 4% AR. SSM followed by IBR as performed in this study has a higher LRR rate compared to regular mastectomy (9-13%) [3,11,31,32] and even to other studies dealing with SSM (2-7%).[21-24,33] Therefore particular emphasis is placed on the evaluation of possible links between risk factors and local regional recurrence rates in patients with SSM and IBR (as done in this study) compared to regular mastectomy in literature in order to optimise patient selection for those women opting for SSM followed by IBR. We are well aware of discrepancies in the LRR rates between different series, mainly due to the use of different definitions of LRR, different distributions of tumour size and other prognostic factors among reported populations. Patients may also be monitored at different time-intervals and assessment for recurrence may differ between studies.

SSM has been advocated as an oncologically safe treatment for invasive breast cancer with CR rates between 3% and 7%.[20-24] Previous studies, however, have mixed patients with invasive and non-invasive carcinomas[21,34], and the follow-up period has been variable. Recently two studies, which included only women with invasive breast cancer, have been reported with a longer follow-up. Kroll et al. reported a CR rate of 7.0% in 114 women who underwent SSM, which was comparable to tumour recurrence after regular mastectomy in 40 women (minimum follow-up of 6 years).[22] In the study of Medina-Franco et al. the CR rate was 4.5% with a minimum follow-up of 3 years (median 73 months) in a group of 173 women who had undergone SSM.[35] This latter study is the only one, which analysed factors associated with CR after SSM; in univariate analysis tumour size, tumour stage, poor tumour differentiation, and negative progesterone receptor status were found to be significant.[35] These findings are consistent with other reports of factors associated with CR after regular mastectomy.[4,11,36-39] In the present study a significant impact on the rate of CR was found only for multifocal carcinoma, and infiltrating carcinoma with multifocal CIS. Manet et al. also reported multifocal carcinoma in a previous study as a predictive factor of local recurrence (LR) after breast conserving therapy.[40] In their study of 605 patients, local recurrences were diagnosed in 13% with a median follow-up of 6.8 years; only histologic multifocality of the primary tumour was found to be significantly associated to skin recurrence. Comparable to our results, patients who experienced primary invasive tumour with histologic multifocality had a 4 times greater risk of developing LR.[40]

The number of involved nodes and number of nodes examined are significant for axillary recurrence (AR).[4,41] In most series, the cumulative risk of AR after full axillary clearance or dissection of the lower and middle parts of the axilla (level I and II) ranges from 0.5 to 3.0%.[5-10] The prognosis in patients with AR is poor.[5-7] The best prognosis for patients with AR are those patients with complete eradication of the AR and those without nodal involvement at time of diagnosis of the primary tumor.[5] In the present study, 4 ARs occurred in 3 women with N0 and in one woman who had not received an axillary dissection. AR occurred three times in an inadequate dissection (i.e. less than 10 nodes removed) and once after removal of 10 lymph nodes. Moreover, because most inadequate axillary dissections were done through a

vertical incision, we changed our policy to do an axillary dissection through a separate axillary incision.

In the present study, all LRR were diagnosed within 6 years after mastectomy and IBR. Most patients with LRR have developed distant metastases; those who have not, had a short follow-up after the diagnosis of LRR. In our study LRR is a significant negative prognostic factor for distant metastasis. In literature the association of LRR of breast cancer with subsequent metastasis is controversial. Some studies indicate that radical local therapy of LRR may decrease the incidence of distant metastases[12,13,18,41,42], but others suggest that local failure is a marker and not a cause of dissemination.[43-45] It has been reported that late recurrences have a better prognosis than early recurrences (i.e. those occurring in the first 2 or 3 years), possibly because an increasing portion of the recurrences will be new primary tumors.[11,19,46-48]

CONCLUSION

In conclusion, the present study shows that histologic multifocal carcinoma and multifocal carcinoma in situ next to the infiltrating component are significant negative prognostic factors for CR after SSM for invasive breast cancer. Although these results need to be confirmed with a larger study population, therapeutic implications of such findings might be the realisation of a regular mastectomy instead of SSM if histologic multifocality of carcinoma or carcinoma in situ is reported.

Furthermore, in case of SSM and IBR we advise to do an axillary dissection through a separate axillary incision instead of the vertical incision as described in this study.

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CHAPTER V

General discussion

SILICONE BREAST IMPLANTS AND SILICONE RELATED SYMPTOM COMPLEX

Silicone breast implants (SBI) were introduced in the early 1960s for breast augmentation and breast reconstruction. Originally, some erroneously thought that silicone was fully inert. However, subcutaneous injection of liquid silicone results in local granulomatous and fibrotic reaction in humans, apes, and mice.[1] These responses were thought to be non-specific and are histologically typical to foreign bodies in general. The local inflammatory response to breast implants is usually minimal. A layer of macrophages may embed the implant, and nearby macrophages have been demonstrated to contain ingested silicone.[2] The intensity of lymphocyte and fibroblast inflammatory response corresponds with the concentration of silicone in the tissue[3] and may directly increase as the molecular weight of the silicone increases.[4] These macrophages and the fibrous tissue reaction around the implant is termed the capsule. However, clinical reports on inflammation and hypersensitivity associated with SBI led to investigations that demonstrated the ability of silicone to induce not only local, but also systemic inflammatory responses.[1] 'Human adjuvant disease' was reported among women who had breast augmentation by injection of paraffin, petroleum jelly, silicone, or unspecified foreign materials.[5,6] Based on a possible association between SBI and undifferentiated connective tissue disease (claimed in different Japanese reports in the 1960s and 1970s), in 1992 the Food and Drug Administration (FDA) banned the use of SBIs in the United States other than for reconstructive purposes or as a part of controlled clinical studies.[7] The hypothesis that SBI might cause rheumatological diseases was based on literature which was limited to case reports and case series at the time of the FDA decision.[8] In 1993 a summary of literature identified 293 reported cases of women who had received SBI with symptoms related to rheumatic diseases.[9] No epidemiological studies were reported at that time.

Since then, many epidemiological studies addressing the potential association between SBI and rheumatic diseases or connective tissue disease (CTD) have been published.[10-24] All these studies, except one[19], have failed to demonstrate an increased risk of CTD; this study found a small, but significant, excess of CTD, based on self-reporting of diseases.[19] The subsequent validation of this study found evidence for overreporting CTD, as only 22.7% of the self-reported cases could be confirmed.[25] Neither of these epidemiological studies has ruled out the possibility that women with SBI might have a complex of symptoms or a syndrome that is not typical of diagnosed CTD. Some investigators have suggested an association between SBI and a new atypical rheumatic condition or atypical CTD that does not fulfil established criteria for any known CTD.[26-29] Solomon et al. evaluated 176 symptomatic patients with silicone breast implants. Nearly 50% of these patients required explantation due to capsular contracture or rupture. They concluded that these observations strongly suggest that local symptomatology might identify a subgroup of women who are at a higher risk for developing systemic disease.[28] At the same time, Borenstein introduced the term siliconosis, a musculoskeletal pain syndrome

characterised by overwhelming fatigue, fever, myalgias and arthralgias.[29] However, no prospective studies on SBI were reported at this stage.

The only way to get an answer to the question of whether or not SBI actually causes (a)-typical CTD or rheumatic diseases, is to follow patients in a prospective manner. Since 1995, every woman who underwent an immediate breast reconstruction with a subpectorally placed silicone prosthesis in the Daniel den Hoed Cancer Centre was prospectively followed according to a defined protocol. The intention of this study was to investigate prospectively the occurrence of complaints related to CTD and rheumatic diseases in relation to antinuclear antibody (ANA) positivity and implant integrity measured by magnetic resonance imaging (MRI).

When a CTD is suspected, the simplest screening test and practical starting point is testing for ANA, which is a test for any autoantibody that binds to non-tissue-specific antigens within the cell. A negative ANA makes the diagnosis of an autoimmune disease highly unlikely, whereas a positive test strongly supports the diagnosis. The finding of an ANA, when combined with the history and clinical examination, may help to confirm a suspected diagnosis of a connective tissue disease or be contributional to various non-rheumatologic conditions in which ANAs develop. In many patients, the symptoms and positive ANAs are judged to be part of an early, undifferentiated rheumatic syndrome in which patience and time are needed to reveal the diagnosis. In some patients, the cause of the ANA is never satisfactorily explained. The presence of ANAs in normal, healthy people has been documented. The frequency generally increases with age: 6% of women in the fertile population[30] and 15-30% of persons over the age of 60 years are ANA positive.[31] Raised titres of ANA have been found in patients with silicone breast implant (SBI).[27,28,32-35] Other studies have found increased reactivity in ANA and other tests for the presence of autoantibodies, but these do not meet the diagnostic criteria for specific autoimmune disease and most studies have addressed small, highly selected groups of patients.[34,36,37] In chapter II.1 among 63 women with SBI, ANA positivity was found in 16% (2-29 months after SBI, mean age at ANA testing was 48 years), which is less than the 20-58% prevalance of ANA reported in other studies.[27,28,32-35] No significant difference in symptom expression between ANA-positive and ANA-negative women was found. A drawback of this study is the retrospective character and that factors influencing ANA positivity, such as age and drugs are not taken into account. Moreover, in chapter II.2 and II.3 no increase in ANA positivity was seen 1 year and minimally 3 years after SBI, compared to preoperative measured ANA. Therefore, it is concluded that within 3 years after SBI implantation there is no increase in ANA expression, which makes the excistence of an CTD in these women very unlikely.

Fryzek et al.[38] recently published the results of a cohort study indicating that women with a cosmetic SBI reported a wide variety of symptoms more often than women with breast reduction surgery. In contrast, few significant differences or consistent patterns were observed in length of time since implantation of the prosthesis and in type (silicone or saline) or volume of the implant. Due to the lack of specificity and absence of dose-response relationships they suggested that the excess of reported symptoms were not causally related to cosmetic

implants.[38] Moreover, two epidemiologic meta-analyses have recently been published.[39,40] The review by Janowsky et al.[39] included 5 discrete diagnoses; i.e. rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, scleroderma, and polymyositis/dermatomyositis and 2 subgroups; i.e. all CTDs combined and other autoimmune or rheumatic conditions were covered.[39] In contrast, the review by Tugwell et al.[40] reviewed another 18 classic/accepted diseases such as Hashimoto thyroiditis, multiple sclerosis, myasthenia gravis, undifferentiated CTD, systemic silicone-related disease and, unlike Janowsky and collegues, reported on numerous signs and symptoms.[40] In both meta-analyses no association was evident between SBI and any of the individual established or atypical CTDs. These reports confirm that there seems to be no evidence for a novel syndrome in women with SBIs, and they concur that epidemiologic evidence suggests that CTDs are not more common in women with SBIs than in women without SBIs. Epidemiologic studies have ruled out a large increase in CTD associated with breast implants, but the status of implants with respect to rupture or extracapsular silicone in these studies was unknown. Reported rates of implant failure range from 4 to 71%, depending on the definition of implant failure, the population base, and the diagnostic method used.[41-44] Factors that are alleged to lead to a higher incidence of implant failure include closed capsulotomy and implant age.[41-44] Implant rupture occurred at a significantly increasing rate with implant age (8 to 15 years).[41-46] MRI of SBI has proven to be a highly sensitive method for visualising both SBI and surrounding tissue, and is more accurate than mammography or ultrasound for detecting implant rupture.[44,47-49] In augmented breast the sensitivity ranged from 75-80% and from 70-75% for MRI and ultrasound, respectively; the specificity for implant rupture is 95% and 90%, respectively.[50-52] Several investigators have reported the presence of various antibodies in the serum of women with silicone breast implants, including anti-silicone antibodies[53,54], anti-collagen auto-antibodies[55,56], and ANAs[27,28,32-36], with the highest antibody levels being found in women whose implants had ruptured or leaked.[33,55] Recently Brown et al. reported on the health status of women with ruptured implants detected by MRI.[57] Extracapsular silicone, diagnosed by MRI, was associated with a significant increase in self-reported physician-diagnosed fibromyalgia (FM). Although this was the first study in which the implant status of all women in relation to self-reported complaints was esthablished, some remarks should be made. First, as in other studies reporting on the relationship between FM and SBI[60-63], the conclusion is based on a small group of patients. Second, because the diagnosis of FM relies on subjective symptoms, the value of the diagnosis FM is questionable.[62,63] Moreover, Jensen et al.[64] recently published a study in which the predominant rheumatic conditions among women with breast implants, were soft-tissue rheumatism and degenerative diseases. However, in their control group, soft-tissue rheumatism, including tendinitis, bursitis and myalgias, was the most frequent diagnosis.[64] In chapter II.2 it is concluded that the significant higher incidence of Sjögren and RA/Raynaud complaints one year after SBI could not be related to loss of implant integrity diagnosed by MRI. No correlation was found between elevated silicone-related symptom expression and changes in the presence of ANA or altered findings

in MRI of the SBI. On the other hand, Gaubitz et al.[65] demonstrated that silicone does leak from breast implants, with 54% of women with ruptured implants having detectable silicone in the liver, compared to 22% of the patients who did not have a ruptured implant. Control patients, who for many years have had renal dialysis using silicone tubes, showed no evidence of deposition in the liver. The patients with evidence of silicone in the liver do not have a higher risk of connective tissue disease nor do they suffer more frequently from a number of general complaints (such as arthralgias, myalgias and sicca syndrome).[65] Moreover, in another recently published study, no significant difference in the serologic parameters, inflammatory (C-reactive protein) and immune indicators (ANA, Antistreptolysin-O, and rheumatoid factor), were shown when comparing preoperative and postoperative laboratory studies in a prospective study of 218 patients with a mean follow-up of 5.8 years.[66] In chapter II.3, it is concluded that, although there was no change in ANA expression 3 years after SBI, RA/Raynaud related complaints were significantly increased. Due to the limitations of this study (no control group) it is not clear whether the elevated RA/Raynaud expression is related to SBI or simply due to increase of age.

It is concluded that women with SBI have more RA-related complaints compared to the preoperative score. Especially stiffness of joints and painful joints are reported significantly more often one year and minimally 3 years after SBI. This increase in complaints did not correlate with an increase in ANA in serum, or in a difference in implant integrity. Therefore, these complaints can not be explained on immunological basis. Nonetheless, women undergoing SBI should be informed about these findings.

PSYCHOLOGICAL ASPECTS OF IMMEDIATE BREAST RECONSTRUCTION WITH A SUBPECTORALLY PLACED SILICONE PROSTHESIS

Although many women currently choose breast-conserving therapy, mastectomy remains a viable option for some. When a mastectomy is the desired or required therapy, breast reconstruction can be a significant adjunct treatment. Understanding options for reconstruction can reduce the psychological impact of impending mastectomy on breast cancer patients.[67]

Women who seek reconstruction tend to be younger than women who do not, and some studies show that they are more likely to be caucasian, well educated, affluent, and married or in a relationship.[68] As the age of women undergoing a mastectomy increased, the number undergoing breast reconstruction decreased. The reason for this could be the influence of family, friends or even the specialist. Reaby's study of Australian women who opted for external prostheses revealed that pressure from family or friends, who believed that breast reconstruction was frivolous and vain at a certain age, figured prominently in their decisions.[67] Moreover, Baker et al. found that 20% of women undergoing mastectomy were not offered reconstruction; for this group, age was a significant factor, as 65% of them were 60 years or older.[69] In addition, a surgeon's attitude regarding reconstructive procedures may also influence

a patient's decision; preoperative discussions on risks benefits and possible outcomes can easily be biased.[70] Women who choose for reconstruction and those who choose for mastectomy alone are difficult to distinguish psychologically before surgery.[71] According to several studies, body image and feelings of attractiveness are generally better with reconstruction[72-76], but aspects of quality of life do not differ.[68,77,78]

Before 1990, it was commonly suggested that women undergoing mastectomy must mourn the loss of their breast before they can obtain psychosocial equilibrium.[79] Furthermore, some maintained that patients forced to live with mastectomy scars before receiving reconstruction would ultimately be more satisfied with the results of their reconstruction.[80] However, others have demonstrated the psychosocial benefits of immediate breast reconstruction (IBR).[76,81,82] This includes less depression, less time to mourn the complete loss of the breast, and not having to endure mutilation while waiting for a second operation.[76,83] Other studies show a decrease in anxiety and depression[84] and a significant better body image, self-esteem and sexual feeling of attractiveness and satisfaction when comparing IBR with delayed reconstruction.[84,85] However, recently, Alderman et al. reported no significant differences in satisfaction between patients undergoing delayed and immediate reconstruction.[86] Based on these data, denying women the option of IBR in the hope of producing greater patient satisfaction does not appear to be justified.

Overall, women are satisfied with their breast reconstruction.[74,76,87,88] The studies described in chapter III.1 and III.2 aimed to determine patients' motivation for and satisfaction with IBR with a subpectorally placed silicone prosthesis after oncological or prophylactic mastectomy. In both studies the most important perceived advantage of IBR was not to have the experience of an external prosthesis. Although this is in accordance with previous research[76,83], it is surprising because the women had no experience at all with an external prosthesis. Obviously, the mere thought of wearing an external prosthesis is enough to warrant choosing for IBR. Although many women have complaints about the reconstruction, the majority was satisfied with IBR after mastectomy and 88% would do it again. Although the prophylactic group was more satisfied, there was no significant difference in satisfaction between the prophylactic and the cancer group. Overall satisfaction is mostly influenced by cosmetics, information and specific prosthesis-related complaints. The women with IBR after oncological mastectomy have significant more cosmetic complaints than those who have prophylactic mastectomy: the reconstructed breast was not similar to the other breast (75% agreed) and was too high (40% agreed) (chapter III.2). Asymmetry can be explained by the (mostly) unilateral oncological mastectomies instead of the (always) bilateral prophylactic mastectomies. This is in concordance with the findings of Ramon et al.[89], in which patient satisfaction with IBR was mainly influenced by symmetry. Furthermore, the satisfaction ratings contrast with the absence of praise for the cosmetic outcome of the reconstruction.[90] Although 30% (chapter III.2) to 58% (chapter III.1) of the women have complaints about the reconstruction, the majority of women are satisfied and make the same choice again. In chapter III.2 special attention is paid to

specific prosthesis-related complaints and satisfaction, i.e. discomfort, pain, tension of the skin, and cold/stiff sensation of the skin of the reconstructed breast. The more specific prosthesis related-complaints the patients had, the lower their satisfaction level was. These findings are similar to those reported by Nissen et al.[90], in which it was concluded that women generally gave high satisfaction ratings even though many reported loss of feeling and hardening of the reconstructed breast.

Although the need for information is weakened (chapter III.1 compared to chapter III.2), the correlation between information and satisfaction remains significantly high. The less satisfied the patients were the higher their need for more information about the results of IBR, the dis/advantages of IBR, and the use of silicone prosthesis. Rosenqvist et al. found high levels of patient satisfaction following immediate reconstruction, although they point out that high levels of preoperative information and psychological support were necessary.[82]

Based on these findings, the importance of specific prosthesis related-complaints and the aesthetic result of IBR should be taken seriously when informing patients about the entire procedure. In the study of Baker et al.[69], 90% of patients adjusted well to mastectomy whether or not they received reconstruction. Women were dissatisfied with their results for two main reasons: first, postoperative scarring and pain; and second, a cosmetic appearance that did not match their expectation. The authors believe that women may have made better choices with more thorough counselling. Highest patient satisfaction is achieved when patients are given realistic expectations of cosmetic, sensory, and functional outcome.

In both chapter III.1 and chapter III.2 it is concluded that satisfaction was significantly correlated with the need for information: the less satisfied the patients were and the more complaints they had, the higher was the need for information, especially information about breast reconstruction and the use of silicone prosthesis. Therefore, it is of major importance to fully inform patients about breast reconstruction, the dis/advantage of immediate breast reconstruction and the use of silicone prosthesis, in order to maximise the patient's chance for eventual satisfaction.

CLINICAL ASPECTS OF MASTECTOMY FOLLOWED BY IMMEDIATE BREAST RECONSTRUCTION WITH A SUBPECTORALLY PLACED SILICONE PROSTHESIS

Morbidity of immediate breast reconstruction with a subpectorally placed silicone prosthesis

The insertion of a silicone prosthesis under the pectoral muscle is the simplest method of immediate breast reconstruction (IBR). In chapter IV.2 the surgical technique and advantages of skin-sparing mastectomy by inverted drip incision and immediate breast reconstruction with a subpectorally placed silicone prosthesis are described in detail. In both chapter IV.1 and chapter IV.2 the complication rate and loss of prostheses are addressed. In chapter IV.1 the role of radiation therapy on complications is described and chapter IV.2 focuses on early

complications after mastectomy with an inverted drip incision and immediate reconstruction in a large series. In literature, the total complication rate of implant reconstruction ranges from 8 to 76%.[91-102] The most early complication is infection (1 to 7%)[102,103], and the latest complication to develop is capsular contraction (5 to 15%).[98,102-106] Loss of prosthesis ranges from 1-16%.[92-94,98,102,107-109] In chapter IV.1 the actuarial probability to lose the prosthesis within 3 years was 10%. Although capsular contracture was the most common complication (21%), this did not contribute to loss of prosthesis to as great a degree as infection or wound necrosis. The main reason for removing the silicone prosthesis was infection (chapter IV.1 and chapter IV.2).

The complication rate in the current series (chapter IV.1 and chapter IV.2) compared well with reported ranges in literature. Therefore, breast cancer patients or women with a high risk for breast cancer can safely (with regard to morbidity) be treated with mastectomy by an inverted drip incision and immediate breast reconstruction with a subpectorally placed silicone prosthesis; however, some remarks about patient selection need to be made.

Late asymmetry, produced by the failure of the reconstructed breast to undergo natural ptosis as the patient ages, could be a reason for the poor late cosmetic result.[102] Based on clinical experience IBR with a subpectorally placed silicone prosthesis is not the method of choice for obese patients and those with ptotic breasts (chapter IV.2).

It is generally established that factors such as obesity, previous radiotherapy and smoking can contribute to complications in reconstructive surgery.[96,97,100,107,108,100] Especially prosthetic breast reconstruction after preoperative or with postoperative irradiation have a substantially higher complication rate than in the non-irradiated breast [97,111-115], capsular contracture in particular.[103,115,116] These findings are similar to the results described in chapter IV.1. The incidence of early complications was higher in the radiation group, but not significantly higher. Capsular contracture occurred significantly more often around prostheses implanted in irradiated area before (P<.0005) and after IBR (P=.001). The appearance of a capsular contracture affects the late result: an often too small and hard breast without natural ptosis.[102] Moreover, loss of prosthesis occurs significantly more often in irradiated women (chapter IV.1), which was also demonstrated by Bareau-Pouhaer et al.[117] These findings have resulted in a change of policy for the treatment of irradiated patients in the Daniel den Hoed Cancer Centre. As the role of radiotherapy will continue to evolve as (adjuvant) treatment in breast cancer [118-120], the use of radiation before and after mastectomy will increase with, subsequently, important implication for breast reconstruction. The use of autogenous tissue with or without a prosthesis is recommended for breast reconstruction in previously irradiated patients and those receiving radiotherapy postoperatively. The effect of radiation on reconstruction performed using myocutaneous flaps has been the subject of several studies.[121-124] Hunt et al.[122] found no significant increase in complications following TRAM flap reconstruction and radiotherapy. Zimmerman et al.[123] found no flap-related complications in 21 patients who had free TRAM flap reconstruction followed by radiotherapy. Moreover, Spear et al.[116] found the latissimus dorsi flap an excellent resource for salving periprosthetic contracture in the implant-reconstructed

radiated breast. In general, if radiotherapy is required, it is sensible to avoid prosthetic-only reconstruction and preferentially resort to autologous breast reconstruction. Myocutaneous flap reconstruction, which offers sufficient blood supply and healthy cover over the irradiated chest wall, does not appear to be affected by previous radiotherapy. Because non-irradiated distant skin is brought into the area of reconstruction as part of the flap, the need to use the already damaged irradiated skin of the chest is obviated.

Prophylactic mastectomy and immediate breast reconstruction in women with a suspected or proven genetic predisposition for breast cancer

Since 1994 genetic testing became an option for individuals from families with a hereditary form of breast cancer and/or ovarian cancer (HBOC), due to the identification of two breast cancer susceptibility genes BRCA1[125] and BRCA2.[126] Together, BRCA1 and BRCA2 are thought to account for 8% of all breast cancers and for 50% of all hereditary breast cancers.[127,128] Women with a BRCA1 or BRCA2 mutation have a cumulative lifetime risk of invasive breast cancer up to 70 years of 55 to 85%.[129,130] In these women the risk of breast cancer begins to increase near the age of 25 years. Their overall survival once breast cancer does develop is similar to that of age-matched patients with sporadic cases of breast cancer. In both, the 10-year survival rate is about 50%.[131,132] Women with the mutation may opt for either regular surveillance; prophylactic mastectomy (PM), or oophorectomy, or both; or chemoprevention. Among BRCA1/2-positive women, PM may reduce the risk of breast cancer by 90%[133,134], tamoxifen may reduce it by 49%[136], and the combination of tamoxifen and prophylactic oophorectomy may reduce the risk of breast cancer by 84%.[136] However, the role of tamoxifen in treating BRCA-positive patients remains to be delineated. It is unclear whether tamoxifen, whose main mechanism of action is that of an anti-estrogen, would be expected to have any effect on BRCA1 patients, whose tumours are frequently estrogen receptor-negative.[137] Efficacy of PM is dependent on the ability to remove nearly all breast tissue. In literature, the method of resecting breast tissue and the indications for PM have been variable and might lead to a false assessment of its efficacy. The majority of series report on subcutaneous mastectomy in which the nipple-areolar complex and its underlying tissue is left behind.[138-143] The recurrence rate of breast carcinoma developing in these series range from 0.3% to 19%. In chapter IV.3 the surgical technique of PM as performed in the Daniel den Hoed Cancer Centre is described. To minimise the amount of residual breast tissue after PM, all breast tissue including the superficial or subdermal fascia, the axillary tail, the nipple-areolar complex and the pectoral fascia are removed. In our study no breast cancer has developed after PM, but the follow-up to date is short.

Although PM does not provide complete protection from breast cancer it remains a reasonable treatment option for patients at high risk of breast cancer. A factor that might overestimate the efficacy of PM includes inadequate risk assessment and marginal indications for surgery. Most studies reporting on the efficacy of PM in women with an increased risk of breast cancer are based on family pedigree and not on DNA testing.[144] A retrospective study at

the Mayo Clinic demonstrated a reduction in breast cancer incidence after PM. With a median follow-up of 14 years, the reduction in breast cancer incidence among patients at high risk for the disease was at least 90%.[145] However, the gene mutation status of the study participants was unknown. Meijers-Heijboer et al.[134] recently published a prospective study on 139 women with a proven BRCA1 or BRCA2 mutation. Half of the women underwent PM and the others chose for regular surveillance. After a mean follow-up of 3 years, no breast cancer was observed after PM, while under regular surveillance 8 incident breast cancers were diagnosed. Although in this latter study the follow-up is short and the number of patients is limited, it is concluded that PM in proven mutation carriers reduces the incidence of breast cancer.[134]

PM rates among carriers range from 3% to 50%.[146,147] Age and parenthood are predictors towards PM in unaffected carriers of the mutation.[146,148] Furthermore, cultural differences in views on health and disease, risk and prevention, paternalism versus autonomy, and feminity might influence interests in PM.[149,150] The introduction of genetic testing for BRCA1 and BRCA2[151], combined with the proven effectiveness of the procedure in mutation carriers[133,134] have the potential to change the patterns of practice for PM. In our clinic women increasingly base their decision for PM on proven susceptibility (chapter IV.3). Overall, since 1998, about 90% of high-risk women based their choice for PM on a proven BRCA1/BRCA2 mutation in contrast to less than 20% before 1996.[146]

Sixty to 97% of women undergoing PM choose for breast reconstruction after PM.[134,151,152] In the Daniel den Hoed Cancer Centre more than 90% of the women undergoing PM, opted for immediate breast reconstruction (chapter IV.3). Although the complication rate of IBR after PM is relatively high (21%), most women (87%) are satisfied with their decision for IBR after PM and would make the same choice again (88%) (chapter III.2).

Oncological aspects of skin sparing mastectomy followed by immediate breast reconstruction with a subpectorally placed silicone prosthesis

Skin-sparing mastectomy (SSM) was introduced in 1991 by Toth and Lappert.[153] It maximises skin preservation in order to facilitate reconstruction of the breast mound and enhances its aesthetics, due to better preservation of the original inframammary fold. SSM and immediate breast reconstruction (IBR) must be a safe oncological procedure that does not lead to an increased number of local recurrences compared with mastectomy alone, neither should it interfere with adjuvant oncologic therapies. Several studies have demonstrated that IBR does not delay the administration of adjuvant radiotherapy or chemotherapy.[109,154-156] It has been suggested by some that early complications of reconstruction might delay chemotherapy[117], but others have refuted this.[155,157-159] For example, in a consecutive series of 52 patients with IBR, no increase in surgical complications or chemotherapy side- effects were found compared to patients undergoing IBR without chemotherapy and patients treated with chemotherapy after regular mastectomy without IBR.[157] In chapter IV.1, only one of the 27 patients who received chemotherapy after IBR had a low grade infection of the skin above the prosthesis during the

first course of chemotherapy, which was adequately treated with oral antibiotics. This did not interfere with the chemotherapy programs.

Local recurrence after SSM ranges from 4-7% after a maximum mean follow-up of 45 months[108, 160-163], which is comparable to the local recurrence rate after regular mastectomy.[164-167] Malata et al.[168] concluded that there is no evidence that immediate reconstruction is associated with higher recurrence rates or interferes with the physical examination during follow-up. In case of a subpectoral position of the prosthesis, theoretically it minimises the possibility of the device masking recurrent disease. However, most recurrences are detected as palpable skin flap masses and therefore immediate autogenous tissue reconstruction after SSM should not interfere with local tumour surveillance.[169]

Risk factors for local recurrences seem to correlate with tumour stage and biological tumour properties.[170] In the study of Medina-Franco et al.[171] the chest wall recurrence rate was 4.5% with a minimum follow-up of 3 years (median 73 months) in a group of 173 women who had undergone SSM. This latter study analysed factors associated with local recurrence after SSM; in univariate analysis tumour size, tumour stage, poor tumour differentiation, and negative progesterone receptor status were found to be significant. These findings are consistent with other reports of factors associated with chest wall recurrence after regular mastectomy.[165,172-176] Several studies have described the experience of SSM for locally advanced breast cancer (i.e. stage IIb and III). The local recurrence rate after traditional mastectomy for locally advanced breast cancer and IBR ranges from 4-14% with a maximum median follow-up of 58 months.[177-180] Recently, Foster et al.[181] found a recurrence rate of 4% after SSM and immediate breast reconstruction by autogenous tissue for locally advanced disease (stage IIb and III). They concluded that SSM with immediate breast reconstruction is a safe technique for locally advanced breast cancer that does not interfere with (neo)adjuvant treatment. In the study presented in chapter IV.4 patients had locally advanced diseases. No significant association between local recurrence and tumour size or nodal status was seen. However, the study samples are too small to make definite conclusions.

In chapter IV.4 the local recurrence rate after SSM is described. Within a median follow-up of 6.1 years after SSM, 10 recurrences (11%) were detected in the native skin flaps and 4 axillary recurrences (4%). SSM followed by IBR as performed in this study has a higher loco-regional recurrence rate compared to regular mastectomy (9-13%)[164-167] and even to other studies dealing with SSM (2-7%).[160-108] Therefore, particular emphasis was placed on the evaluation of possible links between risk factors and local regional recurrence rates in patients with SSM and IBR compared to regular mastectomy in literature in order to optimise patient selection for those women opting for SSM followed by IBR. Multifocal carcinoma (P=.03) and multifocal carcinoma in situ next to the primary tumour (P=.04) were associated with a higher local recurrence. The axillary dissection was significantly more often inadequate (P=0.001) and significant less lymph nodes were removed (P=0.004) when performed through a vertical incision compared to a separate axillary incision (P=0.001).

It is concluded that SSM with IBR has some oncological restrictions. First, SSM is not advised in case of multifocality of carcinoma or carcinoma in situ next to the primary tumour. A regular mastectomy with or without breast reconstruction should be done in those cases. Secondly, axillary dissection should be done through a separate axillary incision instead of the vertical peri-areolar incision.

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CHAPTER VI

Summary and Conclusions

SUMMARY

In chapter I an overview of the treatment of breast cancer and breast reconstruction is presented and an outline of the thesis is given.

In Chapter II the results of the relation between silicone breast implants (SBI) and the silicone-related symptom complex (SRSC) are described. In chapter II.1 a retrospective study evaluates the postoperative prevalence of antinuclear antibodies (ANA) in relation to symptoms related to SRSC. In this study the sera of 63 women with a SBI were tested for the presence of ANA and at the same time they were screened for the prevalence of SRSC by questionnaire at an interval of 15 months (median) after SBI implantation. Sixteen percent of the women were ANA positive. There was no difference in SRSC expression between ANA-positive and ANA-negative women. The lack of difference in symptom expression between the ANA-positive and the ANA-negative women and the rather low SRSC-complaints support the non-existence of a silicone-induced disease. In chapter II.2 a prospective study evaluates the prevalence of the SRSC in relation to ANA and magnetic resonance imaging (MRI) of the SBI. A total of 57 women undergoing immediate breast reconstruction (IBR) after mastectomy with a SBI were tested just before and one year after operation for the presence of ANA in their sera and screened by questionnaire for SRSC-related symptoms at the same time. MRI evaluated all prostheses one month and one year after SBI implantation. One year after SBI implantation women had significantly more Sjögren and rheuma (RA)/Raynaud related complaints. Especially sore eyes and stiffness of joints were significantly more mentioned one year after operation. Changes in complaint-expression were not associated with changes in ANA expression or with MRI changes of the SBI. In chapter II.3 a prospective study evaluates the prevalence of the SRSC in relation with ANA, one year and at least 3 years after SBI implantation. The sera of 75 women were tested for the presence of ANA and these women were screened for the prevalence of the SRSC related symptoms by questionnaire, at three time intervals: just before, one year and at least 3 years after SBI implantation. One year after operation women had more Sjögren-related symptoms, whereas this increase normalised 3 years after SBI implantation. RA/Raynaud related symptoms were significantly more seen one and minimal 3 years after operation. There was no change in ANA expression one year and 3 years after SBI implantation. The rather small patient sample and the short follow-up period after silicone implantation is a drawback of these 3 studies. Nevertheless, the increase in RA/Raynaud related complaints, especially stiffness of joints and painful joints, did not correlate with an increase in ANA or with a difference in implant integrity measured by MRI. Therefore, these complaints can not be explained on an immunological basis. However, women undergoing SBI should be informed about these symptoms.

Chapter III gives an evaluation of patients' satisfaction with IBR with a subpectorally placed silicone prosthesis using a self-report questionnaire which includes (1) demographic details, (2) perceived advantages of IBR, (3) satisfaction with IBR, (4) information and (5) quality of life, body image, and sexual functioning. Some items replicate questions used in previous research, or

excisting scales, or are designed by researchers of this study. In chapter III.1 special emphasis is made on motivation for, information on, and satisfaction with IBR. It studies satisfaction more deeply by relating it to the quality of life, body image and sexual functioning. Seventy-three patients with IBR after mastectomy, completed and returned the questionnaire. Although none of these women had the experience of an external prosthesis, the most reported advantage was not having to wear an external prosthesis. Despite the fact that 50% of the reconstructions results in complications or complaints, 70% of the women were satisfied and only 12% would never choose IBR again. Satisfaction was strongly correlated with the need for information. The less satisfied patients were with IBR, the higher their need was for more information about the results, the advantages and disadvantages of IBR and the use of the silicone prosthesis. Psychological and physical quality of life and body image significantly correlated with satisfaction. Although sexuality did play a role in the choice for IBR, it did not seem to be important for satisfaction with IBR. Women might be dissatisfied with the results of IBR, but their sexual relation is not necessarily unsatisfactory. It is concluded that women undergoing IBR with a subpectorally placed silicone prosthesis need accurate information prior to operation, including the outcome and the (dis) advantages of IBR and the use of a silicone prosthesis in order to avoid disappointments. In chapter III.2 special attention is paid to the differences of IBR after prophylactic or oncological mastectomy. Satisfaction with IBR and specific prosthesis related complaints, such as discomfort, pain, tension, and cold and stiff sensation of the reconstructed breast is studied in detail. Overall 139 women were treated with IBR after mastectomy; 68 women were treated for breast cancer (oncological group) and 71 women had a prophylactic mastectomy (prophylactic group). Comparable to the results in chapter III.1 the most important subjective advantage of IBR for both groups was not having to wear an external prosthesis, which was significantly more frequently reported in the prophylactic group. Despite the fact that one third (31%) of the women had complaints about the reconstruction (38% oncological group, 25% prophylactic group (ns)), 80% of the women were satisfied with IBR and 88% would choose IBR again. There was no significant difference in satisfaction between the prophylactic and the oncological group. Satisfaction was most frequently influenced by cosmetics, information and specific prosthesis related complaints. Especially prosthesis related complaints were important for both the prophylactic and the cancer group. The women with IBR after oncological mastectomy had significantly more cosmetic complaints than those who have prophylactic mastectomy: the reconstructed breast was not similar to the other breast (75% versus 50% agreed) and was too high (40% versus 20% agreed) Although almost all patients received information about IBR, the use of a silicone prosthesis and the (dis)advantages of a silicone prosthesis, a quarter of the women still had the need for more information. The cancer group had a greater need for information than the prophylactic group, although not significantly. Compared to the prophylactic group, different information items were correlated to satisfaction in the cancer group. This can be explained by the difference in decision-making time interval between groups. While women

with high risk for breast cancer had several contacts with different physicians during a period of several months, women with breast cancer only had several weeks to make a decision. When comparing both studies it is concluded that overall the need for information is decreased, but the correlation between information and satisfaction remains high. Therefore, informing patients about the entire procedure with respect to specific prosthesis related-complaints and the aesthetic results of IBR is of the utmost importance.

Chapter IV describes the clinical aspects of IBR, including morbidity, management and oncological follow-up of IBR with a subpectorally placed silicone prosthesis after mastectomy, are described. Details about the surgical procedure are given. Chapter IV.1 evaluates the incidence of local complications after IBR with a subpectorally placed silicone prosthesis. Special emphasis is made on the effect of radiation treatment and IBR. The medical records of 100 women with 115 IBRs with a subpectorally placed silicone prosthesis are reviewed. Thirteen prostheses were implanted prior to radiation treatment, and 15 prostheses were implanted after irradiation of the chest wall. In 71 reconstructions (62%) no complications were observed. Early complications (within 6 weeks after operation), i.e. infection (n=7), wound necrosis (n=5), bleeding (n=3) and haematoma (n=2) were seen in 15% of the IBR and are more often (not significantly) seen in irradiated women. At long term follow up the most common complication was capsular contracture (21%). This occured significantly more around prostheses placed in previously irradiated area ($P<0.0005$), or prostheses which were irradiated after IBR ($P=0.001$). Loss of prostheses was seen in 11 women and was significantly ($P<0.005$) more frequently observed in irradiated women compared to non-irradiated women. The actuarial probability to loose the prosthesis within 3 years was 10 %. Most often, infection and wound necrosis contributed to loss of prosthesis. In this study it is concluded that complications, especially capsular contracture and loss of prosthesis, after IBR with subpectorally placed silicone prosthesis occur more frequently in irradiated than non-irradiated patients. In previously irradiated women the use of myocutaneous flaps for breast reconstruction is recommended. The retrospective study described in chapter IV.2 analyses data on complications and surgical interventions in 356 women who receive 510 mastectomies with an inverted drip incision and immediate reconstruction (MIDIIR) to determine potential prognostic factors of early complications. The postoperative course was uneventful in 82% of the MIDIIR. Early complications (within 6 weeks after operation), i.e. infection (n=32), bleeding (n=31), wound necrosis (n=29), and protrusion of the prosthesis (n=20) were seen in 24% of the MIDIIR, leading to surgical intervention in 55% (11% in total). Age, size of the prosthesis, radiotherapy, previous lumpectomy and the indication for mastectomy were no significant factors for the prognosis of early complications. The complication rate in the current series compared well with reported rates in literature. Therefore, breast cancer patients or women with a high risk for breast cancer can safely (with regard to morbidity) be treated with mastectomy by an inverted drip incision and IBR with a subpectorally placed silicone prosthesis. In chapter IV.3 the management of women with a proven BRCA1 or BRCA2 germ-line mutation or with a 50% risk

of carrying the mutation, who have opted for prophylactic mastectomy (PM) is described. The postoperative complications, especially in combination with IBR, and the preliminary results of the oncological follow-up after PM are also reported. In this study 112 women underwent a PM. Twenty-nine women had been treated for breast cancer, 2 for DCIS and 2 for ovarian cancer. Most women were proven BRCA1 and BRCA2 mutation carriers. At histological examination 4 specimens with DCIS were found. Ninety-two percent of the women opted for IBR following PM. After IBR the complication rate was 21%; 11% within 6 weeks and 10% more than 6 weeks after PM and 10 prostheses (5%) were removed (follow-up: median 3.5 years). The 79 patients with no previous history of breast cancer or ovarian cancer were free of disease after a median follow-up of 2.5 years after PM. Five of the 29 women who were treated for breast cancer before PM were alive with metastatic disease at last consultation. The remaining 24 women were alive without evidence of disease 7.7 years (median) after primary breast cancer diagnosis. All 4 women with DCIS found at pathological examination of PM were alive without evidence of disease 4.0 years (median) after PM. It is concluded that more than 90% of the women undergoing PM opt for IBR. The complication rate and loss of prostheses after PM and IBR are acceptable. Although the follow-up after PM is rather short, no breast cancer has developed until now. In chapter IV.4 the incidence of locoregional recurrence (LRR) and associated risk factors in a population of women who underwent skin-sparing mastectomy (SSM) and IBR with a subpectorally placed silicone prosthesis is examined. A series of 88 women is reviewed with a minimal follow up of 3 years, who received this procedure for stage I (41%), IIa (32%), IIb (15%) and IIIa (2%). Thirty-two percent of the tumours were multifocal carcinomas and 24% had multifocal carcinoma in situ (CIS) next to the primary tumour. When an axillary dissection was done through the vertical peri-areolar incision, significant less lymph nodes were removed and significantly more inadequate dissections were done (P=0.004 and P=0.001 respectively). With a median follow up of 6.1 years after SSM, 14 LLR (15%) were seen: 10 chest wall recurrences (CR) and 4 axillary recurrences (AR). These LRR had developed with a median of 3.7 years after SSM. Multifocal carcinoma (P=0.03) and CIS (P=0.04) were associated with a higher CR rate. LRR was associated with distant metastases (P=0.006) and with a trend towards decreased overall survival (P=0.07). It is concluded that histological multifocal carcinoma and multifocal CIS are significant negative prognostic factors for CR after SSM for invasive breast cancer. In these patients a regular mastectomy is the treatment of choice whether or not followed by IBR. Moreover, axillary dissection should be done through a separate axillary incision instead of the vertical peri-areolar incision.

In the general discussion described in chapter V all the different items of this thesis are discussed comparing them with the most recent literature.

In conclusion:

1. Although 3 years after SBI implantation women have more RA/Raynaud related complaints, no serological change in ANA expression nor changes in implant structure measured by MRI could confirm an immunological background for this increase in complaints.
2. Although one third of the women have complaints about the reconstruction, the majority is satisfied with IBR with a subpectorally placed silicone prosthesis. Satisfaction is correlated with cosmesis, specific prosthesis related complaints and information. Patients have to be informed with realistic information about cosmetic outcome and prosthesis related complaints before operation.
3. The complication rate of IBR with a subpectorally placed silicone prosthesis after mastectomy for breast cancer or prophylactic mastectomy is acceptable. However, some remarks about patient selection has to be made:

   i) Capsular contracture and loss of prosthesis is significantly more often seen in prosthesis implanted in irradiated area before or after IBR. In those cases the use of autogenous tissue for breast reconstruction is recommended.

   ii) Based on clinical experience, IBR with a subpectorally placed silicone prosthesis is not the method of choice for obese patients and those with ptotic breasts.

   iii) SSM (essential for IBR with a subpectorally placed silicone prosthesis) is not advised in case of multifocality of carcinoma or carcinoma in situ next to the primary tumour. A regular mastectomy shall be done in those patients.
4. Axillary dissection should be done through a separate axillary incision instead of the vertical peri-areolar incision, which is used for SSM followed by IBR with a subpectorally placed silicone prosthesis.

SAMENVATTING

In hoofdstuk I wordt in een korte inleiding een overzicht gegeven van de geschiedenis van de behandeling van borstkanker, de ontwikkeling van borstreconstructie en de opzet van dit proefschrift.

De studie betreft vrouwen die na amputatie van de borst een directe borstreconstructie hebben ondergaan door middel van een subpectoraal geplaatste siliconen prothese. In meerdere hoofdstukken wordt nader ingegaan op (1) door siliconen geïnduceerde reumatologisch klachten (hoofdstuk II), (2) tevredenheid met de directe reconstructie (hoofdstuk III) en (3) klinische aspecten van mastectomie gevolgd door een directe reconstructie met een subpectorale prothese (hoofdstuk IV)

In hoofdstuk II worden de resultaten van de relatie tussen siliconen borstimplantaten (SBI) en het siliconen gerelateerde symptoom complex (SRSC) beschreven. Met behulp van (1) een vragenlijst waarin gevraagd wordt naar Sjögren, reuma, Raynaud en niet nader gedefinieerde klachten, samengevat als SRSC, (2) serologisch onderzoek naar de aanwezigheid van antinucleaire antistoffen (ANA) en (3) MRI van de prothese, zijn vrouwen met een SBI preoperatief, 1 jaar en ten minste 3 jaar postoperatief gecontroleerd. Hoofdstuk II.1 beschrijft een retrospectieve studie, waarbij de postoperatieve prevalentie van ANA in sera van 63 vrouwen met SBI vergeleken wordt met uiting van SRSC. Zestien procent van de vrouwen blijkt ANA positief. Er is geen verschil in SRSC klachten tussen ANA positieve en ANA negatieve vrouwen. Het ontbreken van verschil in klachtenpatroon en het relatieve lage percentage van SRSC gerelateerde klachten ondersteunt de veronderstelling dat siliconen geen systemische ziekte induceert. In hoofdstuk II.2 wordt een prospectieve studie beschreven waarin het voorkomen van SRSC in relatie tot ANA en MRI van de siliconen prothesen wordt geëvalueerd. In totaal worden 57 vrouwen met SBI preoperatief en 1 jaar na siliconen implantatie getest op ANA en SRSC gerelateerde klachten. Tevens wordt een MRI verricht van de prothesen 1 maand en 1 jaar na implantatie. Eén jaar na operatie hebben vrouwen significant meer Sjögren, reuma en Raynaud gerelateerde klachten. Met name brandende ogen en stijfheid van gewrichten worden significant vaker 1 jaar na operatie genoemd. Deze verandering in klachtenpatroon is niet gerelateerd aan veranderingen in ANA expressie of MRI veranderingen rond de prothese. In hoofdstuk II.3 wordt de onderzoeksperiode zoals beschreven in hoofdstuk II.2 verlengd met ten minste 2 jaar. In totaal worden 75 vrouwen met SBI voor operatie, 1 jaar en ten minste 3 jaar na operatie onderzocht op het voorkomen van ANA en SRSC gerelateerde klachten. De significante verhoging van Sjögren gerelateerde klachten blijkt na 3 jaar gelijk te zijn aan de preoperatieve waarde. Reuma en Raynaud gerelateerde klachten zijn zowel 1 en 3 jaar na SBI implantatie significant verhoogd ten opzichte van de preoperatieve waarde. Er is geen verandering in ANA expressie 1 en ten minste 3 jaar na operatie. In het algemeen is een nadeel van deze studies de relatief korte vervolgperiode na operatie en het kleine patiëntenaantal. Toch kan geconcludeerd worden dat de toename van reuma en Raynaud gerelateerde klachten,

met name stijve en pijnlijke gewrichten, niet gerelateerd is aan een toename in ANA positiviteit, noch aan verandering in integriteit van de prothese beoordeeld door MRI. Daarom is het zeer onwaarschijnlijk dat deze verandering in klachtenpatroon toe te schrijven is aan een door siliconen geïnduceerde autoimuun ziekte. Vrouwen die een siliconen implantatie ondergaan zullen preoperatief echter wel van deze bevindingen op de hoogte gebracht moeten worden.

In hoofdstuk III wordt nader ingegaan op de tevredenheid over de directe borstreconstructiedoor middel van een subpectoraal geplaatste siliconen prothese, door middel van een vragenlijst met betrekking tot (1) demografische kenmerken, (2) ondervonden voordelen van en (3) tevredenheid over de directe borstreconstructie, (4) informatie over de behandeling en (5) kwaliteit van leven, lichaamsbeeld en seksualiteit. Sommige vragen zijn gebaseerd op gekwalificeerde vragenlijsten, gebruikt in eerder verricht onderzoek, of geformuleerd door de onderzoekers van deze studie. In hoofdstuk III.1 wordt de motivatie voor, informatie over, en tevredenheid met directe reconstructie geanalyseerd. Tevredenheid wordt nader bestudeerd gerelateerd aan kwaliteit van leven, lichaamsbeeld en seksualiteit. In totaal zijn de vragenlijsten van 73 vrouwen, die voor mei 1995 een directe reconstructie ondergingen, geanalyseerd. Ondanks het feit dat deze vrouwen geen ervaring hebben met een uitwendige borstprothese, is het meest genoemde ondervonden voordeel van de directe reconstructie het niet hoeven dragen van een uitwendige prothese. Ondanks dat 50% klachten ondervindt van de reconstructie, is 70% van de vrouwen tevreden met de borstreconstructie en zal 12% niet nog een keer voor deze reconstructie kiezen. Tevredenheid is sterk gecorreleerd aan informatie. Hoe minder tevreden een vrouw met de borstreconstructie is, hoe meer informatie over de resultaten, en de voor- en nadelen van directe reconstructie en het gebruik van siliconen prothese gewenst is. Kwaliteit van leven en lichaamsbeeld correleert significant aan tevredenheid. Ondanks dat seksualiteit een rol speelt bij de keuze voor directe borstreconstructie, is het niet gerelateerd aan tevredenheid. Met andere woorden, ontevredenheid met de borstreconstructie hoeft niet te interfereren met de seksuele relatie. Geconcludeerd wordt dat vrouwen die een directe reconstructie ondergaan met een subpectoraal geplaatste prothese voldoende geïnformeerd moeten worden over de resultaten, voor- en nadelen van directe reconstructie en het gebruik van siliconen prothese, om teleurstellingen te voorkomen. In hoofdstuk III.2 wordt nader ingegaan op tevredenheid over de directe reconstructie bij vrouwen die een profylactische mastectomie hebben ondergaan versus vrouwen die om oncologische reden een borstamputatie hebben ondergaan. Met name wordt gekeken naar prothese gerelateerde klachten, zoals ongemakkelijk gevoel, pijn, spanning, koud en stijf gevoel van de gereconstrueerde borst. In totaal zijn 139 vrouwen, geopereerd na mei 1995: 68 vanwege mammacarcinoom (oncologische groep) en 71 vanwege een verhoogd risico op borstkanker (profylactische groep). Vergelijkend met hoofdstuk III.1 is het meest genoemde ondervonden voordeel van de directe reconstructie in beide groepen het niet hoeven dragen van een uitwendige prothese, dat significant vaker in de profylactische groep genoemd wordt. Ondanks dat 31% van de vrouwen klachten ondervindt van de reconstructie (38% in de oncologische

groep en 25% in de profylactische groep, niet significant), is 80% van de vrouwen tevreden en zal 88% opnieuw voor een directe reconstructie met een subpectoraal geplaatste prothese kiezen. Er is geen significant verschil in tevredenheid tussen beide groepen. Tevredenheid wordt significant beïnvloed door cosmetiek, informatie en specifieke prothese gerelateerde klachten. De vrouwen die om oncologische reden een mastectomie ondergingen, hebben significant meer cosmetische klachten: de gereconstrueerde borst is niet gelijk aan de andere borst (75% versus 50% mee eens) en de gereconstrueerde borst is te hoog (40% versus 20% mee eens). Dit is te verklaren doordat vrouwen in de profylactische groep beiderzijds een mastectomie met reconstructie ondergaan en vrouwen in de oncologische groep een enkelzijdige. Ondanks het feit dat alle vrouwen informatie ontvangen over directe reconstructie, het gebruik van een siliconen prothese, en de voor- en nadelen van een siliconen prothese, heeft 25% behoefte aan meer informatie. Met name de oncologische groep heeft meer behoefte aan informatie. Dit is te verklaren door het verschil in tijdsinterval voorafgaande aan de operatie. Terwijl een vrouw met een verhoogd risico op borstkanker voorafgaande aan de operatie meerdere contacten met verschillende specialisten gedurende meerdere maanden heeft voordat zij een definitief besluit neemt om al dan niet te kiezen tot profylactische mastectomie, heeft een vrouw die vanwege oncologische reden een amputatie moet ondergaan slechts enkele weken om te besluiten tot een directe reconstructie. Wanneer beide studies met elkaar vergeleken worden is de behoefte aan meer informatie verminderd, maar de correlatie tussen tevredenheid en informatie blijft aanwezig. Gebaseerd op deze resultaten, is het van groot belang patiënten voorafgaande aan de operatie duidelijk te informeren over prothese gerelateerde klachten en de esthetische resultaten van de directe reconstructie.

In hoofdstuk IV worden de klinische aspecten, zoals complicaties, management en oncologische follow-up van directe reconstructie met een subpectoraal geplaatste siliconen prothese beschreven. Eveneens wordt uitleg gegeven over de chirurgische procedure. In hoofdstuk IV.1 wordt de incidentie van complicaties beschreven. Speciale aandacht is besteed aan de invloed van radiotherapie. In totaal hebben 100 vrouwen 115 directe reconstructies ondergaan, waarvan 13 protheses in eerder bestraald gebied zijn geplaatst en 15 prothese na implantatie in het bestralingsveld gelokaliseerd zijn. Eenenzeventig reconstructies (62%) zijn ongecompliceerd verlopen. Vroege complicaties (binnen 6 weken na operatie), zoals infectie (7), wond necrose (5), nabloeding (3) en hematoom (2), treden in 15% op en worden meer gezien na bestraling. Op lange termijn (vanaf 6 weken) is de meest voorkomende complicatie kapselvorming (21%), hetgeen significant vaker optreedt rond prothesen geplaatst in eerder bestraald gebied ($P<0.0005$) of nadien in het bestralingsveld liggen ($P=0.001$). Protheseverlies wordt significant vaker gezien bij bestraalde vrouwen ($P<0.005$). Met name wondinfectie en necrose dragen het meest bij aan protheseverlies. Op basis van deze gegevens kan geconcludeerd worden dat bij patiënten die bestraling van de thorax hebben ondergaan, de voorkeur niet uitgaat naar borstreconstructie met behulp van een subpectoraal geplaatste prothese. In die gevallen kan gekozen worden voor een reconstructie met autologe

myocutane flappen. In hoofdstuk IV.2 wordt in een retrospectieve studie nader ingegaan op de complicaties en chirurgische interventies bij 356 vrouwen met 510 directe reconstructies. In 82% is het postoperatieve beloop ongestoord verlopen. Vroege complicaties (binnen 6 weken na operatie), i.e. infectie (n=32), bloeding (n=31), wondnecrose (n=29), en protrusie van de prothese (n=20) zijn opgetreden in 24% en hebben in 11% geleid tot chirurgische interventie. Leeftijd, grootte van de prothese, radiotherapie, voorafgaande lumpectomie, en indicatie voor mastectomie zijn geen significante prognostische factoren voor het optreden van vroege complicaties. Het percentage postoperatieve complicaties correleert met de percentages beschreven in de literatuur. Geconcludeerd kan worden dat vrouwen met mammacarcinoom of met een verhoogd risico hierop veilig (met het oog op vroege morbiditeit) geopereerd kunnen worden door middel van een mastectomie via een verticale incisie gevolgd door een directe reconstructie met behulp van een subpectoraal geplaatste siliconen prothese. In hoofdstuk IV.3 wordt het management beschreven van vrouwen met een bewezen BRCA1 en BRCA2 genmutatie of van vrouwen met een (familiair) verhoogd risico op mammacarcinoom, die kiezen voor een profylactische mastectomie (PM). De postoperatieve complicaties, en de preliminaire resultaten van de oncologische follow-up worden weergegeven. In totaal hebben 112 vrouwen een PM ondergaan, waarvan het merendeel een bewezen genmutatie heeft. In het verleden zijn 29 vrouwen behandeld vanwege mammacarcinoom, 2 vanwege ductaal carcinoma in situ (DCIS) en 2 vanwege ovariumcarcinoom. Bij histologisch onderzoek van de PM preparaten is bij 4 DCIS aangetoond Bij het merendeel van de vrouwen (92%) is PM gevolgd door directe borstreconstructie met een subpectoraal geplaatste siliconen prothese. Na deze ingreep is in 21% een complicatie opgetreden: 11% binnen 6 weken en 10 % nadien. Tien protheses zijn verwijderd (mediane follow-up 3.5 jaar). De 79 vrouwen met een oncologische blanco voorgeschiedenis zijn na een mediane overleving van 2.5 jaar na PM vrij van ziekte. In 5 van de 29 vrouwen met mammacarcinoom in de voorgeschiedenis hebben metastasen ontwikkeld en de overige 24 vrouwen zijn ziektevrij met een mediane overleving van 7.7 jaar na het stellen van de primaire diagnose. Al de 4 vrouwen, waarbij DCIS in het PM preparaat is aangetroffen, hebben geen tekenen van ziekte 4.0 jaar na PM. Geconcludeerd kan worden dat het merendeel van de vrouwen die een verhoogd risico heeft op het ontwikkelen van mammacarcinoom kiest voor een directe reconstructie na PM. Het complicatie percentage van PM met directe reconstructie is acceptabel en alhoewel de follow-up periode kort is, kan lokaal geen mammacarcinoom aangetoond worden. In hoofdstuk IV.4 wordt de incidentie van locoregionaal recidief (LRR) mammacarcinoom en geassocieerde risicofactoren bestudeerd bij vrouwen die een huidsparende mastectomie hebben ondergaan gevolgd door een directe reconstructie met een subpectoraal geplaatste siliconen prothese. De gegevens zijn nagegaan van 88 vrouwen met een minimale follow-up van 3 jaar na mastectomie vanwege een stadium I (41%), IIa (32%), IIb (15%) en IIIa (2%). In totaal blijkt 32% van de carcinomen multifocaal te zijn en bij 24% bleek een multifocaal carcinoma in situ (CIS) naast de primaire tumor aanwezig te zijn. Wanneer een axillaire dissectie via de verticale incisie verricht wordt, worden significant minder

lymfklieren verwijderd en inadequate dissecties verricht (P=0.004 en P=0.001 respectievelijk). Met een mediane follow-up van 6.1 jaar na mastectomie, zijn 14 LLR (15%) gedetecteerd: 10 thoraxwand recidieven (TR) en 4 axillaire recidieven (AR). Multifocaliteit van hetzij carcinoom (P=0.03), hetzij CIS (P=0.04) is geassocieerd met een hoger recidief percentage. Het optreden van LRR is een prognostische factor voor het optreden van metastasen op afstand (P=0.006) en een trend voor een slechtere overleving (P=0.07). Geconcludeerd kan worden dat multifocaal carcinoom of multifocaal CIS een prognostische factor is voor het ontwikkelen van LRR na huidsparende mastectomie voor de behandeling van mammacarcinoom. Bij deze patiënten dient reguliere mastectomie de behandeling van keuze te zijn. Bovendien dient een axillaire dissectie niet via de verticale peri-aureolaire incisie plaats te vinden, maar via een separate axillaire incisie. In hoofdstuk V wordt een algemene discussie gegeven, waarbij de verschillende onderwerpen vergeleken worden met de meest recente literatuur.

Conclusies:

1. Vrouwen hebben 3 jaar na SBI implantatie, significant meer RA/Raynaud gerelateerde klachten, met name stijfheid van gewrichten en pijnlijke gewrichten. Dit is niet gerelateerd aan een toename in ANA positiviteit, noch aan verandering in integriteit van de prothese beoordeeld door MRI. Daarom is het zeer onwaarschijnlijk dat deze verandering in klachtenpatroon toe te schrijven is aan een door siliconen geïnduceerde autoimuun ziekte.
2. Ondanks het feit dat één op de drie vrouwen klachten heeft van de reconstructie, is de meerderheid tevreden over directe borstreconstructie met een subpectoraal geplaatste prothese. Tevredenheid correleert met cosmetiek, prothese gerelateerde klachten, en informatie. Preoperatief moeten vrouwen geïnformeerd worden over de verwachte cosmetische resultaten en de prothese gerelateerde klachten.
3. Het aantal complicaties van directe borstreconstructie met een subpectoraal geplaatste siliconen prothese na mastectomie vanwege mammacarcinoom of profylactische ablatio mammae is acceptabel. Enkele selectie criteria zijn de volgende:

i) Na radiatie van de thoraxwand treden kapselvorming en protheseverlies vaker op. Bij deze vrouwen dient gekozen te worden voor een ander type borstreconstructie, bij voorkeur met autoloog materiaal.

ii) Gebaseerd op klinische ervaring komen obese vrouwen of vrouwen met ptotische mammae niet in aanmerking voor deze reconstructie.

iii) Multifocaliteit van carcinoom of carcinoma in situ is een contra-indicatie voor het verrichten van een huidsparende mastectomie, dat essentieel is voor dit type reconstructie.

4. Axillaire dissectie bij een huidsparende mastectomie dient via een separate axillaire incisie verricht te worden.

DANKWOORD

C'est fini! Met veel plezier heb ik de afgelopen jaren gewerkt aan dit promotie-onderzoek en ben erg blij dat het boekje nu echt voor mij ligt. Meerdere mensen hebben een bijdrage geleverd aan de totstandkoming van dit proefschrift. Enkelen wil ik in het bijzonder bedanken.

Mijn copromotor, Dr A.N. van Geel, Bert, in 1995 maakte ik, naar aanleiding van een publicatie in het NTvG over directe borstreconstructies, een afspraak met je omdat ik daar wel "iets" mee wilde doen in het kader van mijn keuzecoschap. Dat dit zou uitmonden in een promotie had jij eerder door dan ik. Jij wist precies hoe je mij moest aanpakken, "laat die maar schuiven, niet teveel pushen", en met resultaat. Je bent een man van weinig woorden, maar weet hiermee wel de juiste snaar te raken. Ik heb veel zin om nog een tijdje met jou in de DDHK samen te werken.

"The Working Party": Tom Swaak, Inge Marie Obdeijn, Rudi Tjong Joe Wai en Anneke van Wersch, jullie zijn het brein achter de opzet van deze studie en hebben mij volledig vrij gelaten deze naar eigen inzicht uit te voeren. Daar waar nodig stuurden jullie bij.

Anneke van Wersch, dat jij in je hectische leven steeds weer ruimte voor mij wist vrij te maken waardeer ik zeer. De weekendjes in Engeland waren zeer productief en heel gezellig. Jouw enthousiasme voor de psychologie kan zelfs een "botte" chirurg vlijmscherp maken. Je bent een erg mooi mens! It's now time for me to look beyond the borders of your garden, isn't it BJ?!

De leden van de promotiecommissie: Prof. dr. A.M.M. Eggermont, Prof. dr. S.E.R. Hovius, Prof. dr. T. Wiggers, Prof. dr. A. Tibben, Prof. dr. J. Klijn, Prof. dr. H.J. Bonjer en dr. A.J.G. Swaak dank ik voor de interesse in het manuscript en de snelle beoordeling.

Lex Eggermont, de snelheid waarmee jij door de resultaten en conclusies van mijn onderzoek gaat, is zelfs voor mij niet te volgen. Ik dank je voor de mogelijkheden die jij me biedt om me op wetenschappelijk en klinische vlak binnen de chirurgische oncologie te kunnen ontwikkelen.

Theo Wiggers, "promoveren, dat is niets voor jou", was jouw eerste opmerking toen Bert en ik in 1995 langskwamen om het een en ander te bespreken. Een betere stimulans kan je mij niet geven. Je mening veranderde snel en je hebt me prima begeleid tijdens Bert's afwezigheid.

Jaap Bonjer, een opleider van deze tijd, die de gaten in de opleiding weet op te vangen door skills-lab en Ritme en oog heeft voor de werkende moeders. Ik vond het erg leerzaam om de afgelopen 2 jaar onder jouw toezien de hals te mogen exploreren en waardeer het dan ook

zeer dat jij plaats neemt "achter de tafel". Een mastectomie via een verticale incisie is immers minimal invasive.

Ieder artikel in dit proefschrift was telkens weer een heuse bevalling. Ik wil Ronnie van der Holt, Caroline Seynaeve en Laraine Visser bedanken voor hun puntjes op de i.

Het verpleegkundig personeel van A1 en A3, de operatiekamer medewerkers, de dames van het secretariaat chirurgie en de dames van poli 1 zorgen er door hun hartelijkheid voor dat ik iedere keer met veel plezier voor onderzoek en klinische werk in de DDHK terugkeer. Dankzij jullie ben ik een echte Heintje geworden.

Marja van Wijngaarden, secretaresse in hart en nieren, een betere bestaat er niet. Door jouw en natuurlijk ook Marinka's aanwezigheid ben ik het eerste half jaar niet bezweken onder de hitte van het hok, waar het begin is gemaakt voor dit boekje. Ik kon en kan altijd op jou terugvallen wanneer het gaat om handtekeningen, de aanpak van de "mannen", een getypt briefje, statussen, kledingadvies en als luisterend oor voor hoe belachelijk het soms allemaal is.

Sjaan "van de poli", nu echt nooit meer sili I, II en III, vragenlijst I, II, III. Jij hebt er mede voor gezorgd dat de uitval van gegevens tot het minimum beperkt is gebleven; je zat er als een pitbull bovenop. Veel dank hiervoor.

Medewerkers van CLB, afdeling autoimmuunziekte, en in het bijzonder Jan de Jong, wil ik bedanken voor hun gastvrijheid en de begeleiding bij het bepalen van de ANAs

Dr. H.F. Veen, u heeft mij leren omgaan met de klappen van de chirurgische zweep en een degelijke ontgroening gegeven in de wereld die Heelkunde heet. Een betere basis had ik niet kunnen krijgen. Ooit heeft u gezegd dat ik me zou omdraaien in mijn graf als ik dit onderzoek zou laten schieten en dat heb ik in mijn oren geknoopt. In mijn hart staat een grote V en die is niet alleen van Veerle of van Van Brussel.

Mijn paranymfen, Irene Mathijssen en Nelke Manders, jullie vriendschap is niet in een alinea samen te vatten. Irene, mijn coschaptijd in Vlissingen heeft zeker ook iets heel goeds voortgebracht. Ik denk dat jij een van de weinige bent die zich met recht paranymfe mag noemen. Ieder woord in dit proefschrift heb jij gelezen en elk artikel is door jouw voorzien van nuttig commentaar.
Nelke, ik ben blij dat jij verder dan "het medico-meisje met het ijsje" gekeken hebt. Ondanks het contact op afstand volg jij mijn wel en wee op de voet en weet jij precies wat mij bezighoudt. Ik kijk nu alweer uit naar de goeie acties. Ik ben erg trots dat ik 2 van deze sterke karakters naast mij heb op een dag als deze.

Mijn ouders, lieve pap en mam, jullie hebben mij alle vrijheid gegeven in mijn keuzes en mij gestimuleerd me te ontwikkelen tot degene die ik nu ben. Jullie liefde heeft mij in alles enorm gesteund. Het is altijd een beetje vakantie bij jullie in Kamperland!

En last but not least, Jérôme, mijn lieve maatje en Veerle, mijn lieve dochter, het leven is mooi met jullie. Laten we ervan genieten!

Hazerswoude, 20-03-1969, Caroline jij, geboren in de lente, onder aan de dijk, en *"daar glommen de blommen, die zwierden en tierden maar overal, die stonden te blozen en te bloeien, die knikten en knakten en lachten maar al".* Jij was er, je bent er, opgegroeid in het nog ruime Zoeterwoudse land, *"dat land met akkers, tuinen, kleine huizen met open vensters, dat duin, die wei, die hoeve en het vee dat er omheen dwaalt".* Het gaat maar door jouw leven. In 1981, je eerste schooldag op het Stedelijk Gymnasium te Leiden, waar je *"het onderwijs van wijze meesters mag horen, je hebt er vriendinnen en vrienden in, die je met heel je hart bemin, je kunt er veilig wonen, dies zul je je dankbaar tonen".* En al je werken, discipline, en toewijding, resulteren in 1987 tot toegang aan de Erasmus Universiteit in Rotterdam, studie Geneeskunde. Rotterdam, de andere wereld, de stad die met *"tegenwoordigheid van geest en realisme in het kwadraat onomstootbaar feest viert in een opgebroken straat",* waar je in 1992 je doctoraal examen met goed gevolg aflegt. Dan volgen je coschappen, welke je afsluit met een keuzecoschap in Kameroen. In 1995 haal je je basisarts examen, waarna je als AGNIO chirurgie in de Dr. Daniel den Hoed Kliniek gaat werken (hoofd dr. T. Wiggers). In die periode begin je onder begeleiding van dr. A.N. van Geel het onderzoek directe borstreconstructie na mastectomie, dat uiteindelijk resulteert in deze promotie. In 1997 start je de opleiding Heelkunde, te beginnen in het Ikazia ziekenhuis bij dr. H.F. Veen en dr. W.F. Weidema als opleiders. De laatste 2 jaar van je opleiding ben je werkzaam in het Erasmus MC, locatie Dijkzigt, bij opleider Prof. dr. H.J. Bonjer. Aansluitend keer je per maart 2003 met veel plezier terug in de Daniel den Hoed Kliniek als chef de clinique op de afdeling chirurgische oncologie!
Daarnaast doe je met hart en ziel aan muziek en sport. En last but not least: uit de gelukkige verbintenis met Jérôme, je school en soul maatje, is op 14 februari 2002 jullie dochter Veerle geboren!

"En ik trok verder en trok een nieuwe streep en nog een streep en ging weer verder....."

Lieve dochter Caroline: ga jij maar verder, je bent niet alleen.

Mama