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**IMMEDIATE BREAST RECONSTRUCTION WITH
IMPLANTS IN BREAST CANCER PATIENTS**

**ASPECTS OF SURGICAL TECHNIQUE, QUALITY OF LIFE AND
SENSIBILITY**

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Stockholm 2007

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Gårdsvägen 4, 169 70 Solna

To the memory of my mother

ABSTRACT

Breast cancer is the most common form of cancer among Swedish women. The incidence has increased since the beginning of the 1970s. Simultaneously the age-standardized mortality has been relatively constant, which is probably explained by earlier tumour detection as a result of improved diagnostic methods and treatment advances. Most patients have surgery and additional therapy such as radiation, chemotherapy and/or endocrine therapy. For those subjected to mastectomy, a breast reconstruction may be performed either at the time of mastectomy - immediate reconstruction, or at a later date - delayed reconstruction. The standard technique for immediate reconstruction at our reconstructive centre is the use of permanent adjustable prostheses placed under the pectoral muscle. This has been shown to be an oncologically safe procedure with no increased risk of relapse of cancer among the patients.

The overall aim of the present thesis was to attain increased knowledge about the outcome of immediate breast reconstruction with implants. Such knowledge would be guiding in the care of the patients. The perspectives were those of surgical technique, quality of life and breast sensibility.

A long-term follow-up study from a technical aspect recorded several characteristics of the surgical treatment and the patient care. Among the 249 patients operated on between 1990 and 1996, 32 (13 %) had local complications of which eighteen (7 %) lost their prostheses due to infection. Six of these patients lost their prostheses as late as 1-2.5 years after the reconstruction. Three patients had systemic complications.

Improvements in quality of life, one of the major goals in breast reconstructive surgery, were surveyed by use of the Medical Outcome Study 36-item Short Form (SF-36) completed by 76 patients consecutively treated between 1998 and 2001. Preoperative scores for emotional well-being and physical role functioning were lower than in a Swedish reference population, while after 12 months the scores in all domains had improved and were comparable with those in the reference population. The most common reasons for immediate reconstruction were the desire to avoid wearing an external prosthesis and the wish to feel whole again. The women reported great satisfaction with the general outcome of reconstruction and moderate satisfaction with the aesthetic outcome. The major determinant of aesthetic contentment was completion of the reconstructive procedure.

Cutaneous breast sensibility was evaluated retrospectively three to six years after immediate reconstruction and prospectively before surgery and two years after. Von Frey filaments and Termotest[®] were used to assess the sensibility to touch, cold, warmth and heat pain. In both studies all the examined modalities were significantly impaired although some individual sensibility threshold values were comparable with controls. Most affected was the area above the areola. Breast sensibility in patients given postoperative radiotherapy did not differ from the sensibility in those without radiotherapy. Subjectively, the patients reported reduced overall sensibility in the reconstructed breast compared to control. Nearly all patients stated that the reconstructed breast felt different from the other breast; nevertheless two thirds reported that the reconstructed breast felt like a real breast.

In conclusion, immediate breast reconstruction with submuscular implants following mastectomy is associated with a low frequency of systemic and local complications although implants may be lost years after surgery. The women experience an improvement in health-related quality of life over the first postoperative year, reaching levels comparable with the normal population. The reasons for reconstruction are both practical and emotional. The overall cutaneous breast sensibility is significantly impaired which is in accordance with the patients' subjective experience, although the majority reports that the reconstructed breast feels like a real breast, a main purpose of breast reconstruction.

Keywords: Breast cancer, immediate breast reconstruction, implants, complications, quality of life, patient satisfaction, sensibility.

LIST OF PAPERS

The thesis is based on the following papers, which will be referred to by their Roman numerals:

- I.** Jakob Lagergren, Göran Jurell, Kerstin Sandelin, Richard Rylander, Marie Wickman. Technical aspects of immediate breast reconstruction with implants: Five year follow-up.
Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery 2005; 39: 147-152
- II.** Elisabeth Edström Elder, Yvonne Brandberg, Tina Björklund, Richard Rylander, Jakob Lagergren, Göran Jurell, Marie Wickman, Kerstin Sandelin. Quality of life and patient satisfaction in breast cancer patients after immediate breast reconstruction: a prospective study.
The Breast 2005; 14: 201-208
- III.** Jakob Lagergren, Åsa Edsander-Nord, Marie Wickman, Per Hansson. Long-term sensibility following non-autologous, immediate breast reconstruction.
The Breast Journal (In press)
- IV.** Jakob Lagergren, Marie Wickman, Per Hansson. Sensibility following immediate breast reconstruction with implants.
Submitted to Plastic and Reconstructive Surgery

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CONTENTS

LIST OF ABBREVIATIONS.....	8
INTRODUCTION	9
BACKGROUND	10
The breast	10
Breast cancer	10
<i>Epidemiology</i>	<i>10</i>
<i>Classification</i>	<i>11</i>
<i>Risk factors</i>	<i>11</i>
<i>Diagnostic principles</i>	<i>12</i>
<i>Treatment</i>	<i>12</i>
<i>Prognosis</i>	<i>13</i>
Breast reconstruction techniques.....	13
<i>Autologous breast reconstruction / combined reconstruction</i>	<i>13</i>
<i>Non autologous breast reconstruction</i>	<i>14</i>
Immediate breast reconstruction.....	15
Surgical technique.....	16
Quality of life.....	16
Sensibility.....	17
AIMS OF THE STUDIES.....	19
PATIENTS AND METHODS.....	20
Patients.....	20
<i>Study I</i>	<i>20</i>
<i>Study II</i>	<i>20</i>
<i>Study III</i>	<i>20</i>
<i>Study IV</i>	<i>20</i>
Design and methods.....	20
<i>Study I</i>	<i>20</i>
<i>Study II</i>	<i>21</i>
<i>Study III</i>	<i>21</i>
<i>Study IV</i>	<i>22</i>
Statistical methods	23
RESULTS.....	24

Study I	24
Study II	25
<i>Health-related quality of life</i>	25
<i>Preoperative expectations</i>	25
<i>Postoperative satisfaction</i>	27
Study III	28
<i>Touch</i>	29
<i>Cold</i>	29
<i>Warmth</i>	29
<i>Heat pain</i>	29
Study IV	29
<i>Touch</i>	30
<i>Cold</i>	30
<i>Warmth</i>	30
<i>Heat pain</i>	31
GENERAL DISCUSSION	34
Study design considerations	34
Aspects of surgical technique	34
Aspects of quality of life	36
Aspects of sensibility	38
CONCLUSIONS	41
FUTURE RESEARCH	42
POPULÄRVETENSKAPLIG SAMMANFATTNING (POPULAR-SCIENTIFIC SUMMARY IN SWEDISH)	43
ACKNOWLEDGEMENTS	45
REFERENCES	48
PAPERS I-IV	

LIST OF ABBREVIATIONS

ANOVA	Analysis Of Variance
BRCA1	Breast Cancer 1, early onset
BRCA2	Breast Cancer 2, early onset
DCIS	Ductal Carcinoma In Situ
DIEP	Deep Inferior Epigastric Perforator
EBCTCG	Early Breast Cancer Trialist's Collaborative Group
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy-General
LCIS	Lobular Carcinoma In Situ
MBROS	Michigan Breast Reconstruction Outcome Study
QLQ-C30	Quality of Life Questionnaire-Core 30
SF-36	Medical outcome study 36-item Short Form
TMG	Transverse Musculocutaneous Gracilis
TNM	Tumour Node Metastases
TRAM	Transverse Rectus Abdominis Muscle
UICC	Union Internationale Contre le Cancer
WHO	World Health Organization
WHOQOL	World Health Organization Quality Of Life group

INTRODUCTION

The loss of a breast due to cancer surgery is a psychologically traumatic event for many women and influences both mental and physical health [Kemeny et al 1988, Schain et al 1994]. The possibility of having a new breast reconstructed might be consoling, either performed as a delayed procedure one or two years after mastectomy or instantly, at the time of mastectomy - immediate reconstruction. There are several techniques for breast reconstruction such as autologous reconstruction using different microsurgical or pedicled flaps from the abdomen or the trunk and non-autologous reconstruction using implants, adjustable or permanent, with different texture, size and shape. Also combinations of these techniques are available. Immediate reconstruction using expandable prostheses was introduced in the late seventies [Lapin et al 1980] and is now well-established in the surgical treatment of breast cancer.

The standard technique for immediate reconstruction linked to breast cancer surgery at the Karolinska University Hospital is the use of permanent adjustable prostheses placed under the pectoral muscle. Good, consistent results have been achieved with this technique [Wickman and Jurell 1997, Wickman et al 1998, Lagergren et al 2005] and so far nearly 700 patients have been treated.

The main goals of breast reconstruction are to improve well-being and quality of life among breast cancer patients and to achieve a reconstructed breast to feel like a real breast. Also of importance is optimizing the care during the surgery and the post surgery period and to avoid complications. Many patients are concerned about these aspects and raise questions about the outcome of an immediate breast reconstruction. This thesis addresses some of these questions so that hopefully future patients will be better informed about what they can expect from their breast reconstruction.

BACKGROUND

The breast

The female breast is composed of glandular, fibrous and fatty tissues. The glandular component is divided into 15-20 lobes that houses milk producing lobules and ducts for the milk passage. Each lobe is drained by a single duct opening onto the nipple. The gland is located under a vaguely defined subcutaneous fascia arising from the Scarpa's fascia and from this the Cooper's ligaments, which act as fibrous supportive structures between the lobes down to the deep pectoral muscle, arise. The breast extends from the level of the second rib down to the sixth or seventh rib. Medially the breast reaches the sternal border and laterally the tissue may continue into the axilla and reach as far as the latissimus dorsi muscle. Deeply the tissue extends to the pectoral fascia. The blood supply is derived from branches of the internal thoracic artery, the intercostal arteries, and the thoracic branches of the axillary artery. The arteries are accompanied by veins (Figure 1). Also accompanying the arteries is the sympathetic nervous system that innervates the glandular tissue. The cutaneous sensory innervation is derived from branches of the 2nd to 6th intercostal nerves. Lymphatics from the gland are mainly drained laterally to the axillary nodes. Some lymphatics are also drained upward to infraclavicular and supraclavicular nodes, medially to parasternal nodes or the contralateral breast, and inferiorly to extraperitoneal tissues and mediastinal nodes [Hall-Craggs 1985, Hughes and Mansel 2000, Lawson 2002]. During life the female breast undergoes changes in volume, tissue composition and function. Hormones stimulate breast growth in puberty and during pregnancy the glandular tissue is fully developed and functionally activated. After lactation the glandular component is reduced. This relative decline in glandular tissue volume is accentuated in older premenopausal and postmenopausal women following lobular atrophy. The fibrous component is also reduced with age and both glandular and fibrous parenchymas are replaced by fatty tissue [Anastassiades et al 1983, Shekhar et al 2003].

Breast cancer

Epidemiology

Breast cancer is the most common form of cancer among Swedish women and comprises 30 % of all female cancer in the country. Nearly 7000 women are diagnosed per year. The incidence has increased since the beginning of the 1970s with an annual increase of about 2 %. However, the last few years the incidence is stable (153 per 100.000 per year). Breast cancer is age-related and the highest incidence is reached in the interval of 60-69 years (398 per 100.000 per year). 61 % of the patients are 60 years or more when diagnosed with cancer. In the Stockholm region the incidence is at level with that for the whole country and 1500 women are diagnosed yearly [Swedish National Board of Health and Welfare 2007].

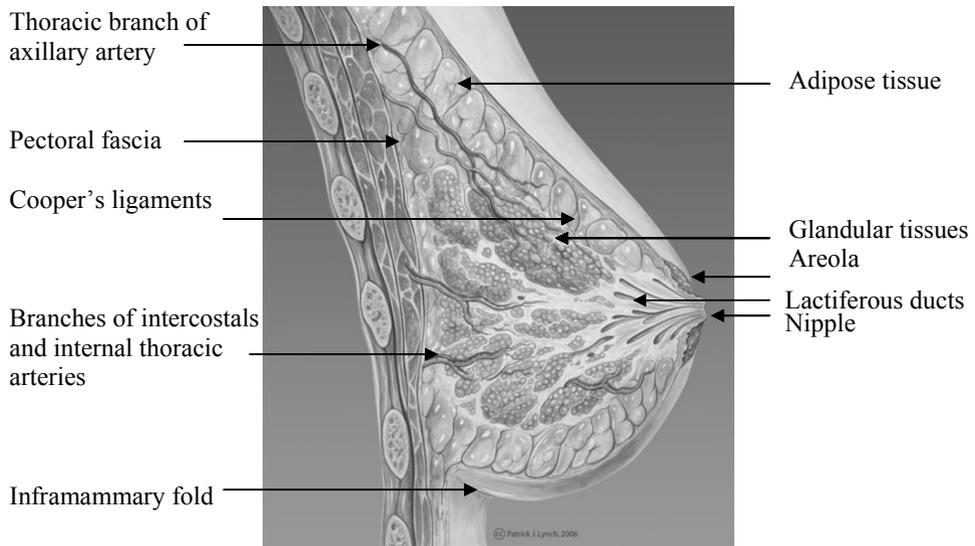


Figure 1. The anatomy of the breast.

Classification

In Sweden breast cancer is classified histopathologically into non-invasive and invasive. The non-invasive subtypes are ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). The invasive cancer is dominated by ductal carcinoma (40-75 %) and lobular carcinoma (5-15 %). Other, rarer invasive subtypes are tubular, medullar, cribriform and mucinous carcinoma [WHO 2003]. The TNM-classification (developed and maintained by the International Union Against Cancer, Union Internationale Contre le Cancer-UICC) is based on the extension and stage of the disease and important in deciding individual treatment and prognosis. The mandatory parameters in TNM-classification are size or extent of the primary tumour (T), spread to regional lymph nodes (N) and occurrence of distant metastases (M). An important complement to the TNM-classification is the histological grade, based on evaluation of specific morphological features. The tumours are differentiated into grade I, II and III and patients with grade I tumours have better survival than those with grade II and III tumours [Elston and Ellis 1991].

Risk factors

Family history of breast cancer is a well-known risk factor for the disease and hereditary breast cancer comprises 5-10 % of all breast cancer cases. Within this group one third is assigned to mutation in one of two known breast cancer genes, BRCA1 and BRCA2 [Miki et al 1994, Wooster et al 1995]. High age, long period between menarche and menopause, low number of pregnancies and high age at first child birth are other well-known factors contributing to a higher risk of breast cancer [Veronesi et al 2005]. Short breast-feeding

periods, overweight, excessive alcohol intake and intake of hormonal substitutes after menopause are other risk factors but these can be prevented [van den Brandt et al 2000, Chlebowski et al 2003].

Diagnostic principles

Symptoms of breast cancer are usually local: A lump or thickening in the breast, a change in the size or contour, a flattening or indentation of the skin or fluid discharge from the nipple. These symptoms lead the patient to a clinical breast examination. The examination, performed by a physician, forms the first part of a triple assessment which also includes imaging investigation and a breast biopsy. Mammography is the golden standard in imaging diagnostics [Tabar et al 2003, Duffy et al 2005] but it is sometimes complemented by other valuable diagnostic imaging tools like ultrasonography [Skaane 1999, Ohlinger et al 2006] and magnetic resonance imaging [Gilles 2003]. The breast biopsy is performed either as a fine needle aspiration biopsy for cytological diagnosis [O'Neil et al 1997] or as a core needle biopsy which allows for histological evaluation [Leifland et al 2003]. This triple diagnostic combination, i.e. clinical examination, imaging investigation and tissue biopsy, has a very high sensitivity with less than 1 % missed cases [Johnsén et al 1980, Leach et al 1995].

Treatment

Treatment exists for every type and stage of breast cancer following national guidelines [Swedish Breast Cancer Group 2007]. Most patients have surgery and additional therapy such as radiation, chemotherapy and/or endocrine therapy. The most common surgical treatment is breast conserving operations: lumpectomies and partial mastectomies (70 %), where only a part of the breast is removed. In patients with large tumours, multicentric invasive or intraductal carcinoma, or inflammatory cancer, a mastectomy is indicated [Veronesi et al 2005]. During a simple mastectomy all breast tissue is removed and during a modified radical mastectomy the breast tissue and axillary lymph nodes to different levels are removed. Sentinel lymph node biopsy is an alternative to a more extended axillary operation [Viale et al 2004, Kim et al 2006]. It is an established surgical procedure with low morbidity for staging of the cancer. If a sentinel lymph node biopsy contains malignant cells an extended axillary dissection is performed and if there are no malignant cells no further axillary operation is needed. Radiotherapy often follows breast conserving surgery for early stage breast cancer in order to reduce risk of local recurrence [EBCTCG 2005]. In general a total dose of 50 Gray is given as fractions of 2 Gray daily, five days a week. To reduce the patients' risk of cancer relapse, adjuvant postoperative systemic treatments may be given [Goldhirsch et al 2005, Veronesi et al 2005]. According to TNM-stage, histological grade and endocrine-responsiveness different chemotherapies or endocrine therapies like the antiestrogen Tamoxifen are given.

Prognosis

More than two thirds of the patients undergoing surgery for breast cancer in Sweden are cured and will not suffer from recurrent disease [Fernö 2004]. The age-standardized mortality among breast cancer patients in Sweden has been relatively constant during the last decades despite the increasing breast cancer incidence. This is probably explained by earlier tumour detection as a result of improved diagnostic methods and screening programmes and also treatment advances [Michaelson et al 2003]. The extension and stage of the disease (TNM-classification) is the most important prognostic factor [Fernö 2004]. The overall 5-year survival is 85 % [Swedish National Board of Health and Welfare 2007].

Breast reconstruction techniques

Breast reconstruction may be performed at the time of mastectomy (immediate reconstruction) or at a later date, usually one or two years after mastectomy (delayed reconstruction). The breast is reconstructed with the patient's own tissue - autologous reconstruction, with implants - non autologous reconstruction, or with a combination of these.

Autologous breast reconstruction / combined reconstruction

In autologous reconstruction the tissue can be transferred as a free flap using microsurgical technique or as a pedicled flap. Donor sites are usually the abdomen, the back or the gluteal region. One of the most common techniques in autologous reconstruction world-wide is the TRAM flap (transverse rectus abdominis muscle flap), either pedicled or free [Holmström 1979, Hartrampf et al 1982, Serletti 2006]. With the pedicled flap, the rectus muscle and the overlying skin and subcutaneous tissue from the abdomen is brought to the mastectomy defect to form the new breast. The flap is based upon the superior epigastric vessels. A free TRAM flap is harvested with the rectus muscle and the attached deep inferior epigastric vessels. This flap is completely separated from the abdomen and brought to the chest defect where it is anastomosed to either the thoracodorsal or internal mammary vessels. The donor defect within the abdominal wall may be repaired with an inlay mesh with both the pedicled and free techniques in order to avoid abdominal wall hernia, a well-known donor site complication [Chevray 2004, Selber et al 2006]. In another frequently used free flap procedure, the transferred tissue from the abdomen is based upon the deep inferior epigastric perforator (DIEP) vessels, and only skin and subcutaneous tissue is used without sacrificing the rectus muscle or fascia [Allen and Treece 1994]. The DIEP flap has shown advantages for the patients compared with the TRAM flap in terms of decreased donor-site morbidity and shorter recovery periods [Gill et al 2004, Garvey et al 2006]. From the upper back the latissimus dorsi muscle with or without overlying fat and skin can be tunnelled under the skin to the mastectomy defect as a pedicled flap based upon the thoracodorsal vessels. This well-

established and widely used reconstructive technique [Olivari 1976, Hammond 2007] is performed as an autologous reconstruction merely or together with a breast implant combining autologous and non autologous reconstructive techniques. Another combined reconstructive technique is that of an implant together with the lateral thoracodorsal flap. This fasciocutaneous transposition flap is raised from the lateral and dorsal aspects of the thoracic wall at the level of the submammary crease to form the lateral part of the reconstructed breast [Holmström and Lossing 1986]. Secondary choices of autologous tissues for reconstruction, when other options are not suitable, are the free gluteal flap [Papp et al 2007] and the free anterolateral thigh flap [Kaplan et al 2003] harvested from the gluteal region and the lower extremity. Disadvantages include the quality of the adipose tissue of the gluteal flap, inferior to that of lower abdominal flaps and the conspicuous donor-site scarring on the anterior thighs. Recently, the free TMG-flap (transverse musculocutaneous gracilis flap) has been advocated as a reconstructive alternative with low donor site morbidity, suitable for selected patients [Wechselberger and Schoeller 2004].

Non autologous breast reconstruction

In non autologous breast reconstruction implants are used to create a new breast mould [Cronin et al 1977]. The implants are usually placed under the pectoral muscle but in some reconstructive centres the preferred placement is subcutaneously in the lower half of the breast [Eskenazi 2007]. The implants vary in many aspects and the spectrum of implant models makes it possible to individually design the reconstruction for each patient. The implants are composed of an outer silicon shell filled with silicon gel, saline or with a combination of these. The volumes range between about 100 cc to about 600 cc. The wall can be smooth or textured. The shape of the implant is anatomical - drop shaped – or round. The height and profile of the prostheses differ. There are adjustable prostheses, temporary or permanent, that are gradually filled with saline until the breast is formed and there are filled, non adjustable permanent implants. The temporary adjustable prostheses are changed to permanent implants in a two-staged reconstructive procedure while the permanent adjustable prostheses are left in place in a single-staged reconstruction. A prosthesis often used for reconstruction in our centre is shown in Figure 2.

In general, autologous breast reconstruction is more demanding than implant reconstruction for both patients and surgeons. Flap procedures result in larger incisions and scars, on the other hand the overall time to complete the reconstruction process may be shorter and the final result, including the breast consistency, better for some patients.

Immediate breast reconstruction

Breast reconstruction at the time of mastectomy has been performed since the 1970s [Snyderman 1980]. It has been shown to be an oncologically safe procedure with no increased risk of relapse of cancer among the patients [Noone et al 1994, Slavin et al 1998, Sandelin et al 2004]. The technique for reconstruction vary in different breast cancer centres and both autologous (TRAM flaps, latissimus dorsi flaps) and non-autologous (implants) techniques are used [Gui et al 2003, Downes et al 2005]. At the Karolinska University Hospital immediate breast reconstruction has been performed since 1990 and nearly 700 patients have been treated. The standard technique at our centre is the use of permanent adjustable prostheses placed under total muscular cover. The patients are identified during weekly breast conferences where oncologists, breast surgeons, radiologists, and cytopathologists meet patients with newly diagnosed breast cancer. The importance of a multidisciplinary team taking care of the patients has been shown [Haward et al 2003, Houssami et al 2006, Singletary 2007]. Patients with inflammatory cancer or known axillary or distant metastases are normally not regarded as candidates for immediate reconstruction. No upper age limit is set. The patients meet a specially trained nurse who also provides written and audio-visual information about the operation. At the time of the consultation the breast surgeon and the reconstructive surgeon meet the patient jointly to discuss and plan for the immediate reconstruction.

In Sweden about 250-300 women undergo immediate breast reconstruction per year which corresponds to 10-15 % of the breast cancer patients that are subjected to mastectomy. This relatively low percentage might partly be explained by the lack of knowledge and misinformation about the risks of breast reconstruction among physicians caring for patients who might be candidates for immediate reconstruction [Wanzel et al 2002].



Figure 2. Textured round permanent adjustable double-lumen prosthesis.

Surgical technique

The mastectomy preceding immediate breast reconstruction is skin-sparing and the aim is to remove all breast tissue. The fascia of the underlying pectoralis major muscle is left in place. The incisions are planned by the breast surgeon and the reconstructive surgeon together considering the tumour site, the size and shape of the breast, and previous scars. The mastectomy is done by the breast surgeon and the reconstruction by the reconstructive surgeon. The skin overlying the tumour is always excised as well as the nipple-areola complex. The reconstruction is usually performed with textured permanent adjustable double-lumen prostheses placed under the pectoralis major and the serratus anterior muscles. The excised breast tissue is weighed to estimate the size of the prosthesis needed and the prosthesis is preoperatively filled with saline to a volume that allows the skin to be closed without tension. A detachable valve is placed superficially in the subcutaneous tissue in the flank. The pectoralis major muscle is restored with absorbable sutures and the skin is closed using interrupted, absorbable sutures in the deep dermis and continuous absorbable sutures intradermal. All patients are given a single prophylactic dose of antibiotics during the operation.

Quality of life

The aim of immediate breast reconstruction is to improve quality of life for breast cancer patients undergoing mastectomy. The concept quality of life – “the overall enjoyment of life” [U.S. National Cancer Institute 2007] is broad and comprises a wide range of aspects like physical, functional, emotional and social well-being. There is no generally accepted definition which instead has led to a variety of definitions. The World Health Organization Quality of Life Group (WHOQOL) includes in its definition aspects such as the individual’s perception, expectations, standards and concerns, physical health, psychological state, level of independence, social relationship, and relationship to the environment [WHOQOL 1995]. Others have defined quality of life as the difference between the patient’s expectations and achievements, the smaller difference the higher being the quality of life [Calman 1984] or have stated that quality of life “refers to patients’ appraisal and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal” [Cella and Cherin 1988]. In this thesis, the term quality of life refers to health-related quality of life which is more specific and probably more appropriate for use in clinical research, as it focuses on aspects of life that are affected by health care interventions [Velikova et al 1999, Bowling 2005].

Health-related quality of life is often measured by the use of written questionnaires completed by the patients. A good quality of life questionnaire should show reliability, validity and responsiveness to clinically significant changes over time [Cox et al 1992, Switzer et al 1999]. There are several such questionnaires developed. Some are disease-specific and address

symptoms and psychosocial complaints that often occur within a particular subset of patients and some are intended for general use, irrespective of the illness or condition of the patient. Examples of the former and widely used are the Quality of Life Questionnaire-C30 (QLQ-C30) developed by the European Organization for Research and Treatment of Cancer (EORTC) [Aaronson et al 1993] and the Functional Assessment of Cancer Therapy-General (FACT-G) scale [Cella et al 1993]. Not disease-specific is the SF-36, a generic measurement tool often used for medical interventions developed by Ware et al [Ware and Sherbourne 1992]. SF-36 consists of eight scales measuring physical well-being, mental well-being, or a combination of these dimensions. In this thesis, the SF-36, adapted to a Swedish population [Sullivan et al 1995], was used for measurement of health-related quality of life.

Sensibility

Cutaneous breast sensibility is likely to be important in the experience of a reconstructed breast. Sensibility emanates from receptor cells that are sensitive to different stimuli. These receptors are specialized neural structures that transform stimulus energy into electric energy, establishing a signalling mechanism in the sensory system [Mountcastle 1980]. The receptors are divided into four classes, each of which is sensitive primarily to one form of physical energy: mechanical, chemical, thermal, or electromagnetic. Information from the receptors is carried through sensory pathways to the brain and conscious awareness. The pathways include neurons that link the receptors at the periphery with the spinal cord, brain stem, thalamus and cerebral cortex [Heimer 1983] (Figure 3). Afferent nerve fibres are categorised depending on their cross-sectional diameter, the degree of myelination and the conduction velocity and each category is associated with different types of sensations. In the primary somatosensory cortex the parts of the body are represented in regions that are related to that part's importance in somatic sensation (somatotopic organization) [Goetz and Pappert 1999]. Each sensory experience consists of four basic attributes, namely modality, location, intensity and time course. Modality defines a general class of stimulus giving rise to a specific type of sensation such as touch, pain, taste or hearing. The location is represented by the set of sensory receptors that are stimulated and active. The intensity depends on the total amount of stimulus energy delivered to the receptors and the timing is defined by how quickly the stimulus energy is received or lost by the receptors [Kandel et al 2000]. All sensory experiences are also dependent upon psychological factors and the context in which the stimulus occurs [Tanner and Swets 1954, Stevens 1975]. The sensory threshold, the lowest stimulus strength at which a subject can detect the stimulus, is the result of the absolute detectability of the stimulus and the criterion that the subject uses to evaluate the stimulus.

Each sensory modality is mediated by a distinct system of receptors and nerve fibres. The neural systems involved in the breast sensibility studies of this thesis were those of touch, temperature, and heat pain.

A number of structurally different receptors mediate the sense of touch. The receptor information is conducted through large-diameter myelinated nerve fibres, A α -fibres and A β -fibres, with a high conduction velocity (30-120 m/s).

The sense of cold and warmth is mediated by thermoreceptors in the skin, cold receptors and warmth receptors respectively. The cold receptor information is conducted through small-diameter myelinated nerve fibres, A δ -fibres, with conduction velocity of 5-30 m/s and the warmth receptor information through small unmyelinated fibres, C-fibres, with low conduction velocity (0.5-2 m/s).

The sense of heat pain is mediated by specialised free nerve endings called nociceptors, widely distributed in the skin and deep tissues. Their information is conducted through small-diameter myelinated nerve fibres, A δ -fibres and small unmyelinated fibres, C-fibres [Kandel et al 2000].

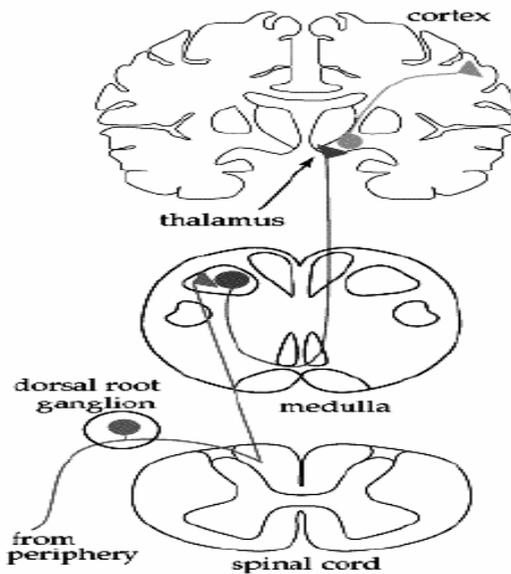


Figure 3. The sensory pathway from the periphery to the brain.

AIMS OF THE STUDIES

The overall aim of these studies was

- to attain increased knowledge about the outcome of immediate breast reconstruction with implants in women with breast cancer or cancer in situ. Such knowledge would be guiding in the care of the patients and would contribute to the prospect of giving the patients facing mastectomy thorough and adequate information about what they can expect postoperatively from an immediate breast reconstruction.

The specific aims were

- to report the long-term results of mastectomy and immediate breast reconstruction with implants from a technical aspect and to see if earlier reported short-term good results were consistent over the years (paper I)
- to assess the quality of life of patients before and after mastectomy and immediate breast reconstruction with implants, to identify the reasons for undergoing the reconstruction and to determine general and aesthetic satisfaction with the result (paper II).
- to evaluate the cutaneous somatosensory status in breasts following mastectomy and immediate reconstruction with implants and to analyze the patients' subjective opinion about somatosensory related percepts in the reconstructed breast, retrospectively (paper III) and prospectively (paper IV).

PATIENTS AND METHODS

Patients

The thesis is grounded on clinical work and the four studies all included patients treated for invasive breast carcinoma or carcinoma in situ. The patients were women undergoing mastectomy and immediate breast reconstruction with implants at the Karolinska University Hospital between 1990 and 2005. The age ranged from 19 to 74 years.

Study I

249 patients with a mean age of 46 years were included. The patients were treated consecutively between 1990 and 1996. The indications for surgery were breast carcinoma (190 patients), carcinoma in situ (30 patients), family history of breast cancer (26 patients), and benign tumour (3 patients).

Study II

76 patients with a median age of 46 years participated. The patients were consecutively treated between 1998 and 2001. The indications for surgery were breast carcinoma (59 patients) and carcinoma in situ (17 patients).

Study III

14 patients with a mean age of 51 years were included. The patients were treated between 1996 and 1999. The indications for surgery were breast carcinoma (6 patients) and carcinoma in situ (8 patients).

Study IV

24 patients with a mean age of 50 years were included. The patients were consecutively treated between 2003 and 2005. The indications for surgery were breast carcinoma (17 patients) and carcinoma in situ (7 patients).

Design and methods

Study I

A retrospective, clinical follow-up study. Follow-up was at least five years in order to evaluate the long-term results of immediate breast reconstruction with implants from a technical aspect. Data about the patients such as age, diagnosis, earlier treatment, type of operations, operating time, hospital stay and complications are consecutively recorded in a database since immediate breast reconstructions were introduced 1990 and these data were retrieved from the database at the time of the study. Data were also retrieved from the

patients' plastic surgery and oncology files. The information was evaluated and presented in paper I.

Study II

A prospective, longitudinal cohort study. The study group was surveyed before surgery and one year after to study changes in health-related quality of life and to assess expectations of and satisfaction with immediate breast reconstruction with implants. The health-related quality of life was measured by the use of the Medical Outcome Study 36-item Short Form (SF-36) [Wear and Sherbourne 1992] completed by the patients. SF-36 has been widely used in medical research throughout the world [Patel et al 2007, Maina et al 2007, Ching et al 2007] and the validity and reliability of the Swedish version is established [Sullivan and Karlsson 1994, Sullivan et al 1995]. Sf-36 consists of eight scales: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health. The first three scales measure physical well-being, while the last three scales relate to emotional well-being. The two scales in the middle are associated with both dimensions although general health perception primarily reflects physical health and vitality primarily reflects emotional well-being. The scales are constructed in such a way that a higher score signifies better health. For each of the eight scales, the score was summed and transformed to a scale of 0-100, representing the percentage of the highest possible score achieved. The results were compared with normative data from an age-matched reference group consisting of 920 women in the general Swedish population.

A study-specific questionnaire, modified from the Michigan Breast Reconstruction Outcome Study [Alderman et al 2000, Wilkins et al 2000] was used to survey the patients' reasons for undergoing immediate breast reconstruction and to survey the postoperative satisfaction with the reconstruction. The preoperative section included 11 possible reasons for undergoing the procedure and the postoperative section comprised five statements concerning general satisfaction and two statements regarding aesthetic satisfaction. Item responses were scored using a five-point Likert scale [Likert 1932] ranging from "agree fully" to "do not agree at all".

Study III

A retrospective, observational study. The cutaneous somatosensory status in breasts following mastectomy and immediate reconstruction was evaluated three to six years after surgery. The untreated contralateral breast served as control. Two points on each breast were examined (Figure 4). The sensibility to touch was assessed by using SenseLAB von Frey filaments (Aesthesiometer, SOMEDIC Sales AB, Hörby, Sweden). The plastic filaments were applied to the skin, which was prodded until the filaments bent 1-2 mm, and were then withdrawn.

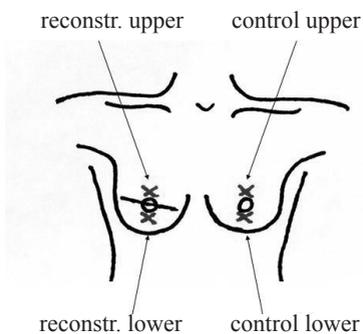


Figure 4. The two points on the reconstructed breast and the control breast respectively that were examined in the quantitative somatosensory testing.

The filaments were applied in a descending order of magnitude to assess the threshold at which sensation disappeared, and in an ascending order to assess the threshold at which sensation appeared. This procedure was repeated four times, and the mean was calculated [Hansson and Lindblom 1993]. A hygrometer recorded the humidity in the room so that a correction for humidity could be calculated, since it affects the von Frey hair-bending threshold [Andrews 1993]. Thermal sensibility was tested with a unidirectional stimulation technique [Hansson et al 1988, Verdugo and Ochoa 1992] using a commercially available device with a Peltier

element-based thermode (Termostest[®], SOMEDIC, Hörby, Sweden) (Figure 5). All measurements started from skin temperature. The perception thresholds for nonpainful cold and nonpainful warmth were obtained by delivering five cold stimuli, followed by five warm stimuli, at a rate of 1°C/sec. The patient was instructed to press the button of a handheld switch to terminate the stimulus at the first sensation of cold or warmth. The average of the five assessments was calculated as the perception threshold for cold or warmth. After assessment of non-noxious thermal perception, the heat pain level was evaluated three times at a stimulus rate of 2°C/sec. The patients were asked to push the button and terminate the stimulus immediately when the heat sensation became painful. To avoid tissue damage, the maximum temperature was set at 50°C. A period of 2 minutes was allowed between the heat pain stimuli to minimize the risk of peripheral sensitization. The average of the last two assessments was calculated as the heat pain threshold.

Before somatosensory testing, the patients completed a questionnaire about their subjective experience of the sensibility in the reconstructed breast. The questionnaire was modified from a somatosensory study earlier conducted at our centre [Edsander-Nord et al 1999]. The questions concerned the patient's experience of touch, thermal and pain sensibility and whether the reconstructed breast felt like a real breast.

Study IV

A prospective, longitudinal cohort study. The cutaneous somatosensory status in breasts following mastectomy and immediate reconstruction was evaluated before surgery and two years after. The somatosensory testing was carried out with the same methods as described in study III with the exception of the von Frey filaments, which were made of optic glass fibre rather than plastic. These optihair von Frey filaments (MARSTOCK nervtest, Marburg,

Germany) are not influenced by normal changes in temperature or humidity [Fruhstorfer et al 2001]. The questionnaire about the patients' subjective experience of sensibility was completed at the two-year follow-up.

Statistical methods

In the descriptive study I no statistical analysis was done except for calculation of percentages and mean and median values.

In study II changes in SF-36 scale scores were analysed using paired t-tests, and for comparisons with the reference population an unpaired t-test was used. Correlations between postoperative satisfaction and clinical parameters were analysed by ANOVA, and forward stepwise regression was used for multivariate analysis.

In study III and IV each value that corresponded to individual yes and no answers for the von Frey filaments was log transformed. The arithmetic means were then anti-log transformed, creating a geometric mean, to better visualize the tactile perception threshold results in a graphic presentation. The Wilcoxon's signed rank test was used when comparing reconstructed breasts with untreated breasts, upper and lower measurement points on reconstructed breasts and the cancer breasts with the noncancer breasts in the same women (related samples). The Mann-Whitney test was used for comparing radiated with nonradiated breasts, larger breasts with smaller ones, and older patients with younger ones (independent samples). $p < 0.05$ was regarded as statistically significant.



Figure 5. The quantitative testing of thermal sensibility was performed with this Termostest[®]-equipment.



RESULTS

Study I

In this follow-up study, technical and postoperative data concerning mastectomy and immediate breast reconstruction with implants were presented. The choice of reconstruction was permanent expander prostheses in 208 reconstructions of 249 performed, permanent prostheses in 32, and temporary expanders followed by permanent prostheses in nine. Various operations were done on the opposite breast at the same time as the reconstruction in 183 patients (73 %) (Table I). The mean operating time was 111 minutes (range 42-195 minutes), permanent prostheses requiring the shortest operating time (mean 90 minutes). Median hospital stay was 5 days (range 2-11), and the median number of outpatient visits was 13 (range 2-46). The patients with permanent expander prostheses had a final total implant volume of 318 ml gel+saline (range 110-770). The expanders were left overexpanded for 8-12 weeks. The median total number of operations for each patient was 3 (range 1-6) with the nipple reconstruction included. The nipple was reconstructed in 192 patients (77 %). The technique for nipple reconstruction varied (Table II). Fifty-seven patients (23 %) were content with only the breast mould and did not want any nipple-areola complex reconstruction. Among the 249 patients operated on, 32 (13 %) had local complications (Table III). Eighteen patients (7 %) lost their prostheses, all of them due to infection. Six of the patients lost their prostheses as late as 1-2.5 years after the reconstruction. There were three systemic complications: two patients developed venous thrombosis in a lower extremity and one patient with severe asthma got a pneumothorax that was treated by drainage.

Table I. Operations on the opposite breast at the time of reconstruction (183/249).

	No. (%) of patients
Reduction	81 (33)
Mastopexy	40 (16)
Mastectomy + prosthesis	38 (15)
Augmentation	13 (5)
Prosthesis after earlier mastectomy	11 (4)
Total	183(73)

Table II. Technique for nipple reconstruction (192/249).

	No. (%) of patients
Nipple sharing	83 (33)
Star flap	49 (20)
Tattooing	34 (14)
Retransplantation	26 (10)
Total	192(77)

Table III. Local complications in 249 patients.

	No.of patients
Loss of prosthesis from infection	18
Infection healed on treatment with antibiotics	6
Bleeding, reoperated	3
Haematoma, not reoperated	4
Persistent local pain	1
Total	32 (13%)

Study II

Health-related quality of life before and 12 months after mastectomy and immediate breast reconstruction with implants was assessed in this study, together with patients' expectations of and satisfaction with the reconstruction.

Health-related quality of life

The patients' mean preoperative SF-36 scores for the four scales primarily measuring emotional well-being (vitality, social functioning, emotional role functioning, and mental health) and for physical role functioning were all significantly lower than those of the reference population. One year postoperatively there was a significant improvement in all these domains except for physical role functioning where the improvement was non significant. At one year, the mean scores for emotional role functioning and mental health were still lower than for the normal population, but for the other scales there was no significant difference. An exception, however, was the domain of bodily pain for which the women in this study scored significantly higher both pre- and postoperatively than the reference population. The patients' SF-36 health profiles compared with those in the age-matched reference population before and one year after surgery are illustrated in Figure 6.

Preoperative expectations

The results of the study-specific preoperative questionnaire are shown in Figure 7. The most common reason for undergoing immediate reconstruction was the desire to avoid the need for an external prosthesis, which was stated as definitely or mostly true by 91 % of the women. The second most common reason was a wish to feel whole again, followed by a wish to enhance self-worth and emotional health.

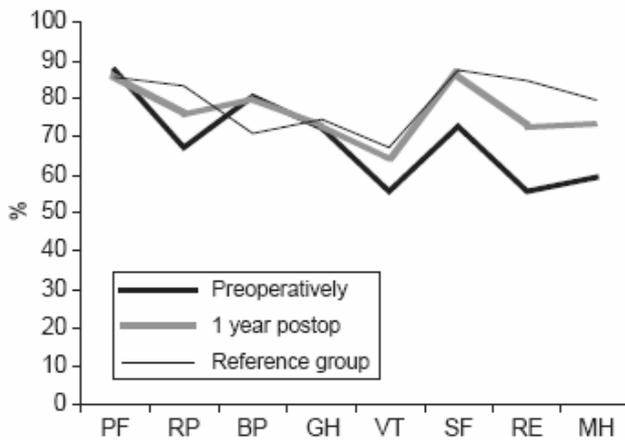


Figure 6. The SF-36 health profile in women undergoing immediate breast reconstruction compared with an age-matched sample taken from the normal population.

PF = physical functioning

RP = physical role functioning

BP = bodily pain

GH = general health

VT = vitality

SF = social functioning

RE = emotional role functioning

MH = mental health

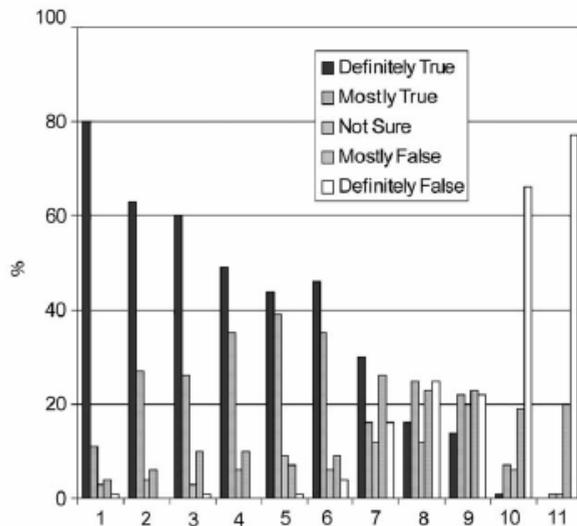


Figure 7. Ranking of reasons for undergoing immediate breast reconstruction, figures in parentheses being percentages of women responding with 'definitely true' or 'mostly true'.

1 = I want to avoid the need to wear a prosthesis (91%)

2 = I want to feel whole again (90%)

3 = I think that immediate breast reconstruction will enhance my self-worth and my emotional health (86%)

4 = I want to wear the same type of clothing I was able to before my breast cancer (84%)

5 = I want to feel attractive (83%)

6 = I want to feel the way I did before my cancer (81%)

7 = I want to have immediate breast reconstruction so that I am not constantly reminded that I had cancer (46%)

8 = I want to be more attractive to my partner (41%)

9 = I want to feel less self-conscious during sexual activity (36%)

10 = I want to improve my relationship with my partner (8%)

11 = I am having an immediate breast reconstruction mainly because my partner wants me to (1%)

Postoperative satisfaction

Figure 8 shows the distribution of responses in the one year postoperative study specific questionnaire. In the general satisfaction section the percentage of women answering definitely or mostly true to the questions ranged between 82 % and 90 %. In the aesthetic satisfaction section corresponding percentages ranged between 50 % and 65 %. In a univariate analysis, incomplete reconstruction was negatively correlated with overall satisfaction ($p<0.03$), with likelihood of recommending the operation to a friend ($p<0.02$), and with aesthetic satisfaction ($p<0.001$). Radiotherapy was negatively correlated with likelihood of recommending the operation to a friend ($p<0.005$) and with aesthetic satisfaction ($p<0.001$). Chemotherapy was negatively correlated with softness of the breast ($p<0.01$). In a multivariate stepwise regression analysis aesthetic satisfaction was strongly associated with completion of reconstruction ($p<0.001$) but not with radiotherapy or chemotherapy.

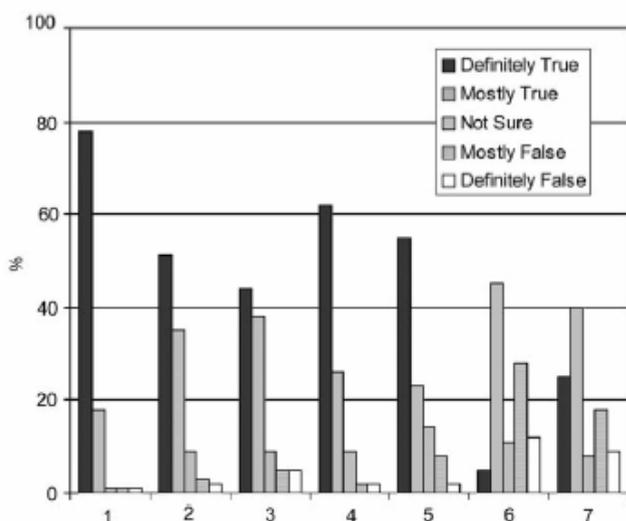


Figure 8. Satisfaction with the reconstruction one year postoperatively. General satisfaction:
1 = Knowing what I know today, I would definitely choose to have an immediate breast reconstruction
2 = Knowing what I know today, I would definitely choose to have the type of reconstruction I had
3 = Overall, I am satisfied with my reconstruction
4 = I would recommend the type of reconstruction procedure that I had to a friend
5 = I felt that I received sufficient information to make an informed choice about my reconstruction options (prosthesis or natural tissue)
Aesthetic satisfaction:
6 = The size and shape of my breasts are the same
7 = My reconstructed breast feels soft to touch

Study III

This study revealed long-term sensibility impairment following mastectomy and immediate breast reconstruction with implants. Three to six years after reconstruction, all the modalities in the quantitative somatosensory testing - touch, cold, warmth and heat pain – were significantly impaired. Least affected was the heat pain modality. In the questionnaire, all patients reported weaker non-modality specific sensibility from the reconstructed breast compared to the control breast. More than half of the patients reported that the reconstructed breast felt like a real breast (Table IV).

	Yes n	No n
$n_{br}=14$		
1. Do you experience any kind of sensibility in your reconstructed breast when touching it, taking a shower, etc?	13	1
2 a. Can you feel pain in your reconstructed breast?	11	3
b. Can you feel touch in your reconstructed breast?	10	4
c. Can you feel temperature (warmth, cold) in your reconstructed breast?	6	8
3. Does your reconstructed breast feel like a real breast?	8	6
4. Does your reconstructed breast feel different from the other breast?	13	1
5. Do you suffer from chronic pain in your reconstructed breast	2	12
6. Do you experience the sensibility in your reconstructed breast as weaker or stronger compared to the other breast?	Weaker 14	Stronger 0

Table IV. The results from the questionnaire in study III, reflecting the patients' subjective experience of sensibility in the reconstructed breast.

	Yes n	No n
$n_{br}=24$		
1. Do you feel any sensation in your reconstructed breast when touching it, taking a shower, etc?	24	0
2 a. Can you feel pain in your reconstructed breast?	22	2
b. Can you feel touch in your reconstructed breast?	23	1
c. Can you feel temperature (warmth, cold) in your reconstructed breast?	20	4
3. Does your reconstructed breast feel like a real breast?	16	8
4. Does your reconstructed breast feel different from the other breast?	23	1
5. Do you experience the sensation in your reconstructed breast as weaker or stronger than that before the operation?	Stronger 0	Weaker 24

Table V. The results from the questionnaire in study IV, reflecting the patients' subjective experience of sensibility in the reconstructed breast.

Touch

There were statistically significant impairment compared to the control breast both above ($p=0.001$) and below the areola ($p=0.001$). The median threshold differed by 5 g for the point above the areola and by 3 g for the point below. One patient lacked touch sensation at the point above the areola on the reconstructive side and four patients at the point below (Figure 9a).

Cold

The sensibility to cold was significantly impaired both above ($p=0.002$) and below ($p=0.01$) the areola. The median threshold differed by 8°C for the point above the areola and by 5°C for the point below compared to the control breast. Two patients lacked cold sensation at the point above the areola on the reconstructive side and three patients at the point below (Figure 9b).

Warmth

The perception thresholds for warmth were significantly impaired both above ($p=0.001$) and below ($p=0.001$) the areola compared to the control breast. The median threshold differed by 13°C for the point above the areola and by 7°C for the point below. Eight patients lacked warm sensation at the point above the areola on the reconstructive side and five at the point below (Figure 9c).

Heat pain

The perception thresholds for heat pain were significantly impaired for the point above the areola compared to the control breast ($p=0.001$). The median value differed by 3°C. For the point below the areola the difference was also 3°C but the significance was borderline ($p=0.05$). Eight patients lacked heat pain sensation at the upper point on the reconstructive side and six patients at the lower point (Figure 9d).

Study IV

This prospective study confirmed much of the results demonstrated in the smaller, retrospective study III. Using quantitative somatosensory testing, the sensibility to all the examined modalities was significantly impaired two years after mastectomy and immediate reconstruction. The impairment was most pronounced in the measurement point above the areola. Some individual threshold values were comparable with preoperative control threshold values. Patients given postoperative radiotherapy ($n=9$) did not differ from patients without radiotherapy ($n=15$) regarding any of the sensory modalities. In a post hoc analysis, the group of patients with resected tissue weights of more than the median (355-1115 g, $n=12$) was compared with the group with resection weights below the median (140-346 g, $n=12$).

Preoperatively, at the upper measurement point these groups showed a significant difference regarding sensibility to touch ($p=0.02$) and a difference with borderline significance regarding cold and warmth ($p=0.05$) with better sensibility in the group with smaller resection weights, i.e., smaller breasts. At the lower point no differences were seen. Two years after reconstruction there were significant differences regarding sensibility to touch ($p=0.007$), cold ($p=0.02$), warmth ($p=0.01$), and heat pain ($p=0.02$) at the lower measurement point in favour of the group with smaller resection weights. No differences were noted at the upper measurement point. Also, as a post hoc analysis, the group of patients older than the median age (52-69 years, $n=12$) was compared with the group younger than the median age (33-51 years, $n=12$) and no significant differences in the examined modalities were found two years after the reconstruction.

In the questionnaire, all twenty-four patients reported reduced sensibility in the reconstructed breast compared to that preoperatively. Twenty-three patients stated that the reconstructed breast felt different from the other breast; nevertheless sixteen reported that the reconstructed breast felt like a real breast (Table V).

Touch

The sensibility to touch was significantly impaired both above and below the areola ($p_{\text{upper}}=p_{\text{lower}}<0.001$) (Figure 10a). The median threshold differed by 7 g for the point above the areola and by 3 g for the point below. Six patients lacked touch sensation at the point above the areola and three patients at the point below. Of these, two patients lacked this sensation at both points.

Cold

The sensibility to cold was also significantly impaired both above and below the areola ($p_{\text{upper}}=p_{\text{lower}}=0.001$) (Figure 10b). The median threshold differed by 7°C for the point above the areola and by 3°C for the point below. Six patients lacked cold sensation at the point above the areola and four patients at the point below. Of these, two patients lacked cold sensation at both points.

Warmth

The perception thresholds for warmth were significantly impaired both above and below the areola ($p_{\text{upper}}=p_{\text{lower}}<0.001$) (Figure 10c). The median threshold differed by 12°C for the point above the areola and by 7°C for the point below. Eleven patients lacked sensation of warmth at the point above the areola and nine patients at the point below. Of these, seven patients lacked this sensation at both points.

Heat pain

The perception thresholds for heat pain were significantly impaired both above ($p_{upper}=0.002$) and below ($p_{lower}=0.005$) the areola (Figure 10d). The median value differed by 2°C for both points. Eleven patients lacked heat pain sensation at the upper point and nine patients at the lower point. Of these, eight lacked heat pain sensation at both points.

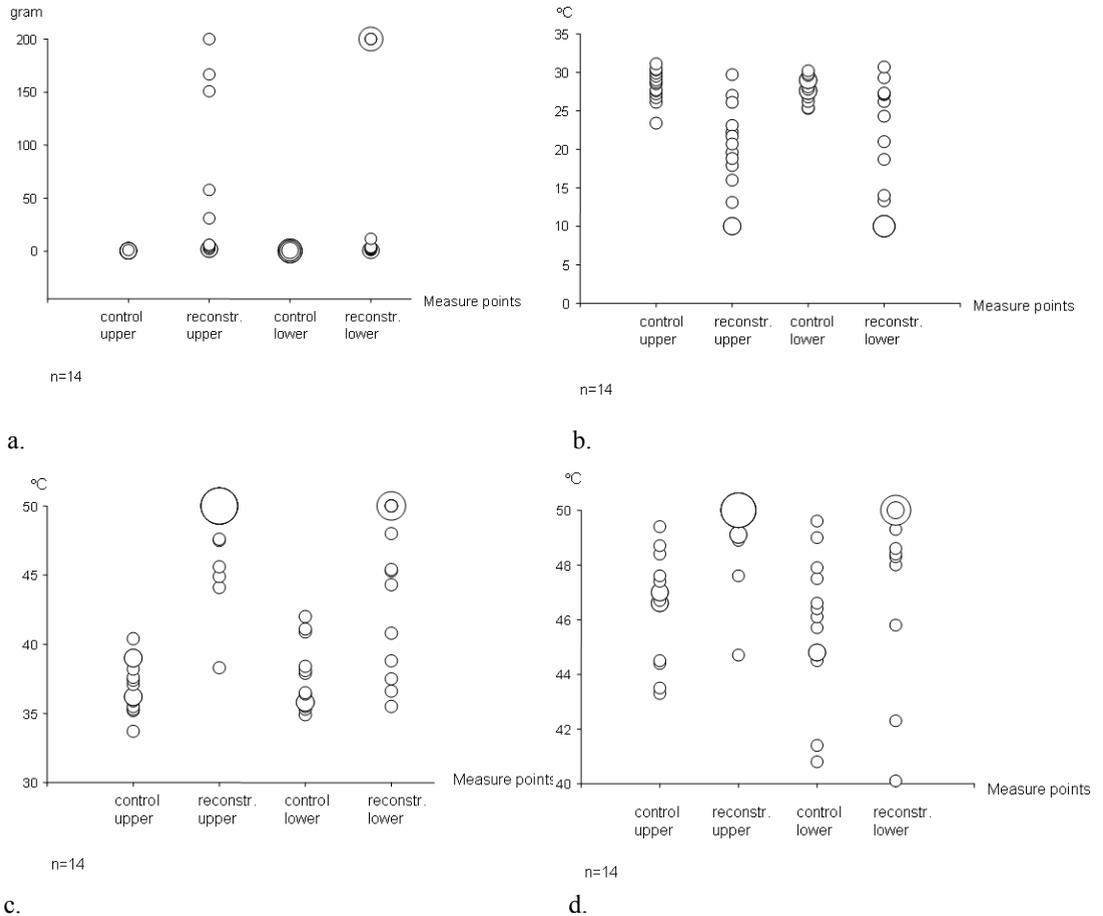
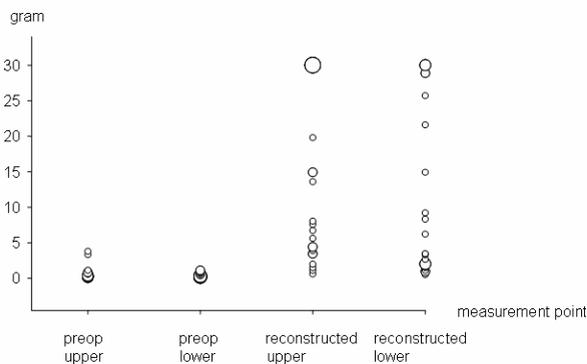


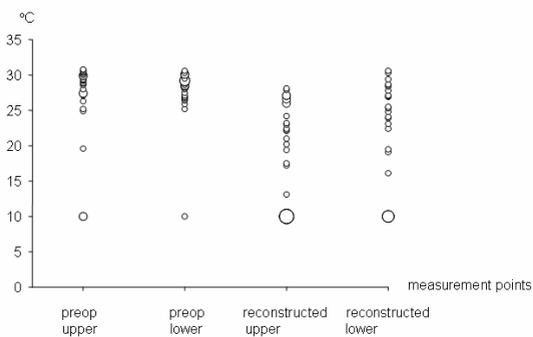
Figure 9. The perception thresholds in the reconstructed breast (reconstructed upper and lower) compared to the control breast (control upper and lower) in study III. The areas of the circles represent number of patients at different levels. Patients devoid of any sensation are depicted in the figures at the maximum values concerning touch, warmth and heat pain and at the minimum value concerning cold.

- a. Touch perception thresholds** ($p_{upper} = p_{lower} = 0.001$)
- b. Cold perception thresholds** ($p_{upper} = 0.002, p_{lower} = 0.01$)
- c. Warmth perception thresholds** ($p_{upper} = p_{lower} = 0.001$)
- d. Heat pain perception thresholds** ($p_{upper} = 0.001, p_{lower} = 0.05$)



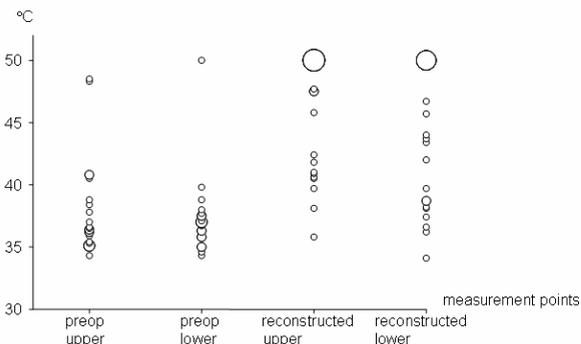
n=24

a.



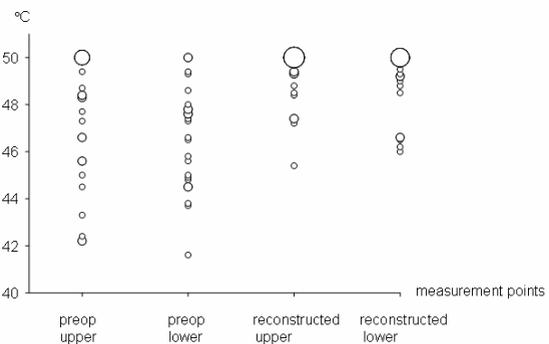
n=24

b.



n=24

c.



n=24

d.

Figure 10. The perception thresholds in the reconstructed breast (reconstructed upper and lower) compared to those preoperatively (preop upper and lower) in study IV. The areas of the circles represent number of patients at different levels. Patients devoid of any sensation are depicted in the figures at the maximum value concerning touch, warmth and heat pain and at the minimum value concerning cold.

a. Touch perception thresholds ($p_{upper} = p_{lower} < 0.001$)

b. Cold perception thresholds ($p_{upper} = p_{lower} = 0.001$)

c. Warmth perception thresholds ($p_{upper} = p_{lower} < 0.001$)

d. Heat pain perception thresholds ($p_{upper} = 0.002, p_{lower} = 0.005$)

A patient who had mastectomy and immediate reconstruction with a permanent adjustable prosthesis (Figure 11).

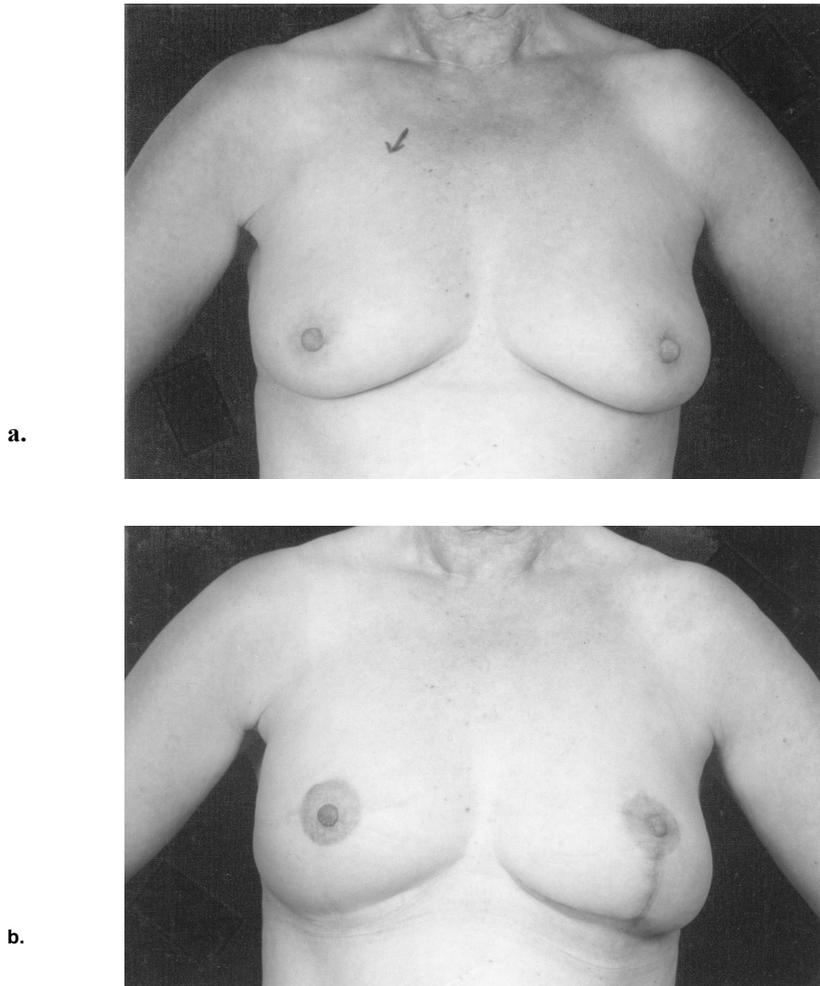


Figure 11. A 60-year-old woman who had a mastectomy and immediate reconstruction with permanent adjustable prosthesis on the right side and a mastopexy on the left side. Later on nipple-sharing and tattooing of the areola was done. (a) Anterior preoperative view and (b) anterior postoperative view, 8 months after the primary operation.

GENERAL DISCUSSION

Study design considerations

This research project aimed to reflect different aspects of immediate breast reconstruction with implants and comprised four studies of which two were prospective. Prospective studies usually have fewer potential sources of bias and confounding than retrospective studies and are therefore generally considered to be of higher research quality [Webb et al 1978, Koop and Strang 2002, Guller 2006]. However, if the outcome of interest is uncommon or the research time is limited a prospective investigation may not be feasible. In study I, the aim was a long-term technical follow-up of minimum five years. Since all patients have been recorded consecutively in a database and our department is the centre for breast reconstructions in the region, with high patient compliance, estimated errors due to lost cases were low and the retrospective design was justifiable. Nevertheless, a surgical centre assessing its own results without an independent evaluator is a potentially source of bias due to misclassification although the first author was not involved in the care of any of the participating study patients. Study III, assessing breast sensibility, was also retrospective and considered as a pilot study in a so far unexplored research field. It was followed by a larger, prospective study (study IV) with similar outcome. In study III, a central point in design was to reach high quality of the controls, although the number of eligible study candidates was reduced. The focus on good controls (non-operated, non-irradiated contralateral breasts) might have been a risk for selection bias, favouring patients with smaller, non-ptotic breasts, not requiring a contralateral operation to attain symmetry. Also in this study, the absence of an independent evaluator could have been a risk for bias due to misclassification.

In all prospective studies, there are also sources of bias that should be avoided such as the loss of individuals to follow up. In the prospective quality of life study (study II), the participation rate at follow up was between 81 % and 88 % and in the prospective breast sensibility study (study IV) the follow-up rate was 80 %. Since these rates are high, selection bias due to losses of cases should not have been a major problem.

Aspects of surgical technique

The optimal time to perform breast reconstruction has been debated. Several studies have shown advantages of immediate reconstruction against delayed, especially for psychological reasons [Schain et al 1985, Al-Ghazal et al 2000] but also for reasons such as cosmetic outcome [Gabka et al 1998] and cost benefit [Khoo et al 1998]. In a single stage, immediate reconstruction completes most of the surgical treatment the patient will require for her breast cancer. Compared to a delayed procedure, the patient is spared one hospitalization and the need to live with the deformity caused by mastectomy. Today, the mastectomy is skin-sparing

which refers to a standard mastectomy aimed at minimizing unnecessary skin sacrifice of the breast. Preservation of breast skin unaffected by tumour provides an ideal colour and texture match of the reconstructed breast with the opposite breast. The oncological safety is well documented [Kroll et al 1997, Sandelin et al 2004]. Any major differences between immediate and delayed reconstruction concerning technical complications have not been reported except for an occasional study where the complication rate was in favour of a delayed procedure, irrespective of type of reconstructive technique used [Alderman et al 2002]. Comparisons have also been made between autologous and non-autologous techniques for immediate reconstruction. The reports are divergent. While some report similar results for both procedures concerning aesthetic outcome but higher failure rate for implant reconstruction, others report better aesthetic outcome for autologous reconstruction but longer recovery period compared with nonautologous reconstruction [Carlson et al 2001, Fogarty et al 2004, Mosahebi et al 2007].

Postoperative radiotherapy might impair the outcome of reconstruction and even have implications on the timing and choice of reconstruction. Especially implant reconstruction has been associated with poorer outcome in terms of higher complication and failure rates when followed by irradiation [Evans et al 1995, Krueger et al 2001, Tallet et al 2003] but also autologous reconstructions suffer from the effect of radiotherapy [Javaid et al 2006]. In many reconstructive centres worldwide there is a hesitation towards the use of prostheses in immediate reconstruction when postoperative radiotherapy is anticipated. In study I of this thesis, patients who had radiotherapy were slightly overrepresented in the reconstruction failure group. However, a vast majority of the patients going through radiotherapy had an uneventful reconstructive procedure with implants. Consequently, in our centre, we still use implants in patients at risk for postoperative radiotherapy, as the patient can have an acceptable breast reconstruction, also shown by others [Cordeiro and McCarthy 2006].

The use of submuscular permanent adjustable prostheses has been the standard for immediate reconstruction in our department. Autologous reconstructive techniques are mostly reserved to secondary reconstructions because of our good experience with implants in immediate reconstruction. We find the method reliable, related to few local and systemic complications and associated with a high degree of patient satisfaction [Rosenqvist et al 1996, Mullan et al 2007]. Also, the patients generally have a short recovery period.

Total submuscular placement of the implant is compulsory since it is associated with lower incidence of capsular contracture than subcutaneous placement [Gruber et al 1981] and allows for reliable postoperative tumour follow-up. Initially, before permanent adjustable prostheses became available, temporary expanders were used with the need to be exchanged to permanent implants at a later stage. Interestingly, in recent years, new attention has been paid to this technique using crescent-shaped temporary expanders. The aim would be more

pronounced expansion of the lower breast pole and improved anatomical breast shape [Eriksen and Stark 2006].

The opposite breast was adjusted to achieve symmetry in most of the patients in study I at the time of reconstruction. This made it possible to match the expanding breast with the remaining one and perhaps spared the patient an additional operation. However, an ideal breast reconstruction would not bring the need for an opposite correction at all, although some patients welcome this adjustment.

The low rate of local complications reported in study I may partly be explained by familiarity with the reconstructive technique and years of reconstructive experience within the surgical team. There have been earlier reports noting more complications at the beginning of the surgeons' experience with a new technique, suggesting a learning curve [Noone et al 1985, Van Heerden et al 1987].

The reconstruction failures resulting from infection surrounding the implants sometimes occurred years after reconstruction. These late failures indicate that the patients need possibility to contact their reconstructive centre at short notice for a long time after the operation, to be able to save the reconstruction if an infection suddenly develops. Few systemic complications were noted and this is in accordance with other reports [Elberg et al 2000]. Factors such as low median age, healthy state except for the breast disease, and good compliance among the patients leading to early mobilization may contribute to this finding.

Aspects of quality of life

Although recurrence of cancer and fear of recurrence have great impact on quality of life among cancer patients [Oh et al 2004], the possibility of enhanced psychological well-being and body image through reconstructive surgery should not be underestimated. Development of new reconstructive techniques and devices has made it possible to create a new breast that can come close in form and appearance to mimic a natural breast. In immediate reconstruction, the patient wakes up with a breast mould already in place, being spared the experience of seeing herself with no breast. "The sooner the better" was stated by Schain et al 1985 regarding optimal timing for breast reconstruction following mastectomy. The authors concluded that patients who had immediate or early reconstruction (within a year after mastectomy) had significantly less recalled distress about their mastectomy than those who had reconstruction more than one year after breast removal (delayed reconstruction). These findings are still valid and the advantages of immediate reconstruction on quality of life have been confirmed by others. Al-Ghazal et al reported in 2000 that patients recalled less distress and better psychosocial well-being following immediate reconstruction compared with patients undergoing delayed reconstruction. In the prospective Michigan Breast Reconstruction Outcome Study (MBROS), women who underwent delayed reconstruction scored significantly lower on a preoperative body image scale than did patients who

underwent immediate reconstruction [Wilkins et al 2000]. No such difference was detected 12 months after surgery which indicates the benefit of immediate reconstruction in that way these women do not go through a period of poor body image. However, there are also studies that have presented data not unanimously in favour of breast reconstruction in relation to quality of life. Nissen et al reported in a prospective study 2001 that patients having mastectomy without reconstruction had significantly less mood disturbance and better well-being than women who underwent mastectomy with reconstruction, 12 and 18 months after surgery.

In comparisons of psychosocial outcomes between different surgery groups, it is also interesting to include patients undergoing breast conserving surgery. A prospective study performed by Harcourt et al 2003 compared women who underwent mastectomy alone, breast-conserving surgery or mastectomy with reconstruction. The quality of life after 12 months was similar regardless of type of surgery. However, body image was enhanced with the latter two procedures. Similarly, a retrospective cross-sectional study comparing psychosocial outcomes in patients undergoing lumpectomy, mastectomy alone or mastectomy with reconstruction reported enhanced body image in the lumpectomy group and the reconstruction group with the most positive outcome for the lumpectomy group. There was no difference between the three groups concerning scores for quality of life [Rowland et al 2000].

In this thesis, the SF-36 questionnaire was chosen as the tool for measuring health-related quality of life. The SF-36 is a generic measurement tool, not disease-specific and intended for general application in medical interventions. It is widely spread and used in quality of life research throughout the world which makes it possible to compare results between studies. Also the availability of a Swedish version and its' well-known validity and reliability were important factors in the choice of this survey.

The women in study II of the thesis, undergoing mastectomy and immediate reconstruction, scored significantly lower for emotional well-being and physical role functioning in the preoperative SF-36 questionnaire compared to the reference population. This was expected since these women were recently diagnosed with breast cancer and facing a major operation. By one year postoperatively, a marked improvement had occurred in all domains assessed by SF-36, comparable with that of the reference population. The lowest scores were those for mental health and emotional role functioning, possibly reflecting an ongoing fear of cancer recurrence. These results are comparable with those recorded in the earlier mentioned Michigan Breast Reconstruction Outcome study (MBROS). MBROS is one of the few prospective studies comparing psychosocial outcome for women undergoing reconstruction in relation to timing of reconstruction and procedure type (autologous vs. implant). As in our study, women undergoing immediate reconstruction demonstrated significant gains in all assessed psychosocial subscales from the SF-36 survey one year postoperatively. The

response did not vary by procedure type. The current study differed from MBROS in the respect that in MBROS the results were not compared with results from a reference population.

The most common motivation women reported for undergoing immediate reconstruction was avoidance of the need to wear an external prosthesis. The inconvenience with an external prosthesis and the improvement in these disturbances following breast reconstruction is well documented [Korvenoja et al 1998]. The wish to be rid of the external prosthesis was also one of the most common motivations for breast reconstructive surgery in a study from Schain et al 1985. Nearly equally important as motivation for reconstruction in our study was the wish to feel whole again and to retain self-esteem. The women wanted reconstruction for themselves rather than for their partners. A wish to improve marital and sexual relations seemed to be of less importance, something that has been verified in other studies [Reaby 1998].

Aspects of sensibility

Although cutaneous breast sensibility is most likely important in the patient's acceptance of a reconstructed breast, it is a neglected aspect of the outcome assessment of implant reconstructions. Studies have focused on patient satisfaction, aesthetic outcome, long- and short-term complications, and oncologic outcome while sensibility has been paid little attention. Autologous reconstructions however, have been evaluated in this context, as have other breast surgery procedures such as breast reduction. In autologous reconstruction early reports concerned the creation of a breast mould and survival of the transferred tissues. As survival rates improved and more flap techniques were developed, the focus shifted toward minimizing morbidity and improving aesthetic outcomes and gradually the interest for sensibility aspects was raised. Some patients who had undergone flap reconstruction complained of pain, and local anaesthesia was required for nipple-areola reconstruction, and from these findings Lehmann et al first performed a sensibility study in 1991 demonstrating spontaneous return of sensation following TRAM flap reconstruction. Later on, other studies have recorded some return of sensibility modalities like touch and temperature, following a variety of autologous breast reconstructions [Shaw et al 1997, Delay et al 2000]. No comparisons between autologous reconstructions and implant reconstructions are available in this aspect, although it would be of interest to survey differences in sensibility outcomes for different techniques and to what extent such differences influence the patients' satisfaction with the reconstruction.

In breast reduction surgery, there are several sensibility studies presented. The overall results have been inconsistent and variable. Most studies have recorded impaired sensibility following reduction, at least for a transient postoperative period [Greuse et al 2001], but there are also reports of improved sensibility [Harbo et al 2003], which is surprising since surgery in general has a negative impact on sensibility outcome. An inverse relationship between

sensitivity and breast size has been reported, i.e. small breasts seem to be more sensitive than large breasts [Tairyach et al 1998, DelVecchyo et al 2004] which was also seen in a post hoc analysis comprised in this thesis (study IV).

To be informed about the lack of protective sensibility following breast surgery is essential for the patients. Accidental second- and third degree burn injuries to breasts reconstructed with autologous tissue have been reported, up to five years postoperatively [Maxwell and Tornambe 1989, Beckenstein et al 1997, Nahabedian and McGibbon 1998].

Study III and IV of this thesis have, for the first time, recorded the sensibility outcome following mastectomy and immediate reconstruction with submuscular implants. In our experience, patients subjected to mastectomy and immediate reconstruction are interested in what they can expect from the operation as far as sensibility is concerned, breasts being an important part of the female body. Except for a single study from 1997, assessing touch sensibility after subcutaneous mastectomy and implant reconstruction [Benediktsson et al 1997], this research field has so far been unexplored. The results in the current studies of the thesis strongly corresponded to each other and demonstrated significant impairment for all the examined sensibility modalities two years or more after reconstruction. The sensibility was more affected above the areola than below. This might be explained by the surgical dissection, which is more extended in this direction both in the mastectomy and in the submuscular dissection, interrupting sensory nerve fibers emerging from the intercostal nerves in two anatomic planes. Despite strong statistical significance on a group level confirming the sensibility impairment, there were some patients who had perception thresholds in the reconstructed breast comparable to the control values. This range of sensibility alterations might be explained by biological variation in the reinnervation capacity. In study IV, the group of patients who had postoperative, locoregional radiotherapy was compared with the group without radiotherapy. Interestingly, there were no significant differences found for any of the somatosensory modalities at the two-year follow-up. In several studies irradiation has been shown to have a negative effect on the outcome of breast reconstructions, especially reconstructions with implants, regarding for example complication rates and aesthetic results [Krueger et al 2001, Chawla et al 2002, Cordeiro et al 2004, Ascherman et al 2006]. This study showed no additional sensibility impairment due to radiotherapy.

Although not in the primary aim of study IV, but of clinical interest, comparison between groups with different breast volumes was made. The sensibility results favoured the group of patients with smaller breasts, both preoperatively and at the two- year follow-up and these data are supported by other studies as mentioned earlier.

Both in study III and IV, the patients' subjective experience of sensibility was surveyed using questionnaires. All patients, except one who didn't experience any sensibility at all, reported impaired overall sensibility in the reconstructed breast and all except two reported that the

reconstructed breast felt different from the other breast. Despite this, nearly two thirds reported that the reconstructed breast felt like a real breast indicating that sensibility impairment is not decisive for this experience. Other factors, such as the consistency and shape of the breast, are possibly important for the integration of the new breast.

Having a design with good controls and consistent follow-up was important. In the retrospective study III the patients' unaffected contralateral breast was ideal as a control, although the number of eligible study patients was reduced since the majority of the potential study group was operated on that side or had received radiotherapy. In study IV, the breast to be reconstructed was used as a control. The patients were followed-up at a minimum of two years after the reconstruction when most alterations in somatosensory function should have taken place as judged from clinical observations and neurophysiologic expertise. The follow-up time was kept as precise as possible to enhance the quality of the study. In the prospective study the two-year follow-up was accomplished with a mean of 24.9 months.

CONCLUSIONS

- Immediate breast reconstruction with submuscular implants following mastectomy is associated with a low frequency of systemic and local complications, even after a follow up of minimum five years. However, implants may be lost years after surgery, which is why long-term follow up is essential for outcome measures.
- Women with breast cancer or cancer in situ undergoing immediate breast reconstruction with implants after mastectomy experience an improvement in health-related quality of life over the first postoperative year, reaching levels comparable with the normal population. The reasons for reconstruction are both practical (wish to avoid the need to wear an external prosthesis) and emotional (wish to feel whole again). The women are very satisfied with the general outcome of the immediate reconstruction and moderately satisfied with the aesthetic outcome.
- The overall cutaneous breast sensibility is significantly impaired following mastectomy and immediate reconstruction with submuscular implants. This is in accordance with the patients' subjective experience of weaker overall sensibility in the reconstructed breast. Patients should be informed about this effect preoperatively to allow adequate expectations regarding the sensibility outcome. Despite the sensibility impairment, the majority of the patients report that the reconstructed breast feels like a real breast, one of the main purposes of breast reconstruction.

FUTURE RESEARCH

During the work with this thesis it was obvious that the sensibility aspect of immediate breast reconstruction with implants was a neglected area of research. Surprisingly, no earlier studies were available although breast sensibility should be attached great significance in the outcome of reconstruction. One important aim of more focused research in the field would be to identify differences in expected outcomes between reconstructive alternatives and to be able to inform patients facing mastectomy and reconstruction about these differences. Also of interest would be to evaluate different primary surgeries for breast cancer concerning sensibility outcome. A study that compares patients undergoing mastectomy with or without immediate reconstruction would be of interest, as well as comparisons with breast conserving surgery, in order to estimate to what extent the reconstructive part of the operation affects the sensibility in the breast.

Another interesting and poorly explored research field is long-term cosmetic outcome in reconstructive breast surgery. Except for one occasional study [Clough et al 2005] little has been investigated. What happens to an implant reconstruction in the long perspective? Is the reconstruction stable or will it deteriorate? To what extent does the patients' aging influence the reconstruction outcome? Are the patients equally satisfied ten years after reconstruction as they were the first postoperative year? How is the health-related quality of life changed? To address these questions, a large long-term follow-up study assessing aesthetics and quality of life is now prepared in our reconstructive centre.

Development of reconstructive techniques and progress in materials and devices for implant surgery brings the need for studies, to evaluate and compare new techniques with established ones. Also advances in breast cancer treatment such as intraoperative irradiation and brachytherapy will affect breast reconstruction outcomes and will require research with the aim of optimizing future reconstructions.

POPULÄRVETENSKAPLIG SAMMANFATTNING (POPULAR-SCIENTIFIC SUMMARY IN SWEDISH)

Bröstcancer är den vanligaste cancerformen hos svenska kvinnor och omkring 7000 kvinnor drabbas varje år. Förekomsten har ökat årligen sedan 70-talet samtidigt som dödligheten varit relativt konstant vilket sannolikt beror på att tumörer upptäcks allt tidigare med hjälp av förbättrade undersökningsmetoder och att behandlingsmetoderna utvecklats. De flesta patienterna genomgår en operation och får ytterligare behandling såsom strålning, cellgifter och/eller hormoner. Den vanligaste operationen är en bröstbevarande operation vilket innebär att endast en del av bröstet tas bort och formen och storleken på bröstet förblir till stora delar desamma. Patienter som har en större tumör eller tumör inom flera delar av bröstet måste få hela bröstet borttaget. En återuppbyggnad av bröstet (rekonstruktion) kan då göras antingen i direkt anslutning till bröstborttagandet – omedelbar rekonstruktion – eller vid ett senare tillfälle, oftast ett till två år efter bröstborttagandet – senarelagd rekonstruktion. På Karolinska Universitetssjukhuset används permanenta expanderproteser som placeras under stora bröstmuskeln vid de omedelbara bröstrekonstruktionerna. Efter operationen fylls proteserna successivt med koksaltlösning till dess bröstet får rätt volym och form. Metoden har visat sig säker ur tumörsynpunkt och det finns ingen ökad risk för canceråterfall hos de patienter som genomgår rekonstruktion.

Syftet med avhandlingen var att få ökad kunskap om resultatet av operationsmetoden omedelbar bröstrekonstruktion med protes. Sådan kunskap skulle vara vägledande i omhändertagandet av patienterna och öka möjligheten att kunna ge patienterna information om vad de kan förvänta sig av operationen. Operationsmetoden studerades avseende komplikationer, livskvalitet och bröstkänsl. Förbättrad livskvalitet är kanske det viktigaste målet för en bröstrekonstruktion och känslan har sannolikt stor betydelse för hur patienten upplever och kan acceptera det nya bröstet. Fyra studier genomfördes.

I studie 1 redovisades fakta om 249 patienter som opererats mellan 1990 och 1996 med en minsta uppföljningstid på fem år. Uppgifterna hämtades från en databas och från patienternas journaler och visade bland annat vilka protestyper som hade använts, hur långa operationstiderna var, hur länge patienterna vårdades, hur många operationer som behövdes för att färdigställa rekonstruktionen och på vilket sätt bröstvårtan rekonstruerades. Av de 249 patienterna fick 32 (13 %) komplikationer i operationsområdet varav 18 (7 %) förlorade sina proteser på grund av infektion runt proteserna. Sex av patienterna förlorade sina proteser så sent som 1-2,5 år efter rekonstruktionen. Tre patienter fick mer allmänna komplikationer som kunde behandlas.

I studie 2 mättes hur livskvaliteten förändrades av operationen med hjälp av ett frågeformulär kallat SF-36 som fylldes i av patienterna före rekonstruktionen och ett år efter. De 76 patienter som deltog och som opererades mellan 1998 och 2001 hade lägre livskvalitetspoäng för bland annat känslomässigt välbefinnande före operationen jämfört med en stor svensk kontrollgrupp. Ett år efter operationen hade livskvaliteten förbättrats och var i nivå med kontrollgruppens. I studien undersöktes också varför patienterna ville genomgå rekonstruktion och hur nöjda de blev efteråt. De vanligaste skälen för rekonstruktion var önskan att slippa bära en lös bröstprotes och önskan att få känna sig hel. Kvinnorna var mycket nöjda med det totala resultatet av rekonstruktionen och något mindre nöjda med det estetiska resultatet.

Studie 3 och 4 utvärderade hudkänslan i det rekonstruerade bröstet. Känslan för kyla, värme och värmesmärta undersöktes med hjälp av särskild apparatur kallad Termotest[®] och beröringskänslan mättes med nylontrådar av olika tjocklek kallade von Frey filament. I studie 3 gjordes undersökningarna tre till sex år efter rekonstruktionen och i studie 4 strax före operationen och två år efter. Samtliga känselkvaliteter försämrades av operationen jämfört med före eller jämfört med det andra, obehandlade bröstet. Sämst känsel noterades i övre delen av det rekonstruerade bröstet. Patienter som fick strålbehandling hade inte sämre känsel än de som inte fick strålbehandling. Patienterna upplevde själva att känslan totalt sett var försämrad och nästan alla tyckte att det rekonstruerade bröstet kändes annorlunda än det andra bröstet. Ändå upplevde två tredjedelar av patienterna att det rekonstruerade bröstet kändes som ett riktigt bröst.

Sammanfattningsvis medför omedelbar bröstrekonstruktion med protes relativt få komplikationer men en av de allvarligaste – att patienterna förlorar sin protes – kan inträffa upp till ett par år efter operationen på grund av infektion. Patienterna upplever en förbättrad livskvalitet under det första året efter rekonstruktionen och når nivåer likvärdiga med normalbefolkningen. Skälen för att genomgå rekonstruktionen är såväl praktiska som känslomässiga. Bröstkänslan försämras av operationen vilket patienterna också själva upplever även om de flesta tycker att det rekonstruerade bröstet känns som ett riktigt bröst, vilket är ett av huvudmålen med en bröstrekonstruktion.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to all those who supported me during this research and contributed to the thesis. My special thanks go to:

Marie Wickman, my principle supervisor and head of the Department of Plastic Reconstructive Surgery, for your excellent supervision and support. I am especially grateful for your unfailing, always rapid support whatever the matter is; research, clinical or personal.

Per Hansson, my co-supervisor, for your thorough guiding in sensibility research and for your welcoming way, understanding and support.

Lars-Ove Farnebo, Head of the Department of Molecular Medicine and Surgery, for your encouragement and for providing a first class research department.

Bertil Hamberger, professor of the Department of Molecular Medicine and Surgery, for your support during the different phases of my research.

Georg Klein and **Pierre Åman**, for introducing me to science and research.

Göran Jurell, friend and former head of the Department of Reconstructive Plastic Surgery, for employing me and teaching me the secrets of breast reconstructive surgery.

Marianne Beausang-Linder, friend and former head of the Department of Reconstructive Plastic Surgery, for successful collaboration in difficult department matters.

Kerstin Sandelin, co-author and colleague, for your decisive research advice and for your warm friendship.

Åsa Edsander-Nord, co-author and friend, for teaching me somatosensory testing and for all nice and humorous bickering.

Jessica Gahm, research colleague and friend, for all nice chats about our studies.

Bo Johansson and **Gerd Engholm**, for all your unselfish help with the laboratory equipment.

Bo Nilsson, for valuable help with statistical review and **Pernilla Viklund**, for all help in statistical and administrative matters.

Anders Ljung, friend and my closest colleague, for all your support, wisdom and knowledge and for all our joyful and successful operations during the years.

Håkan Glimåker, friend and colleague at the Department of Surgery, Falu Hospital, for introducing me to plastic surgery and for teaching me the grounds of this craft.

Ann Lindén and **Tina Björklund**, specialist nurses at our outpatient clinic, for your thorough and skilful patient care, your help with the studies and for all fun we have.

Ulrika Kernen, for always being an invaluable help in editing and computer matters - a rock solid.

Torbjörn Holm, colleague at the Department of Surgery, for our stimulating collaboration in rectal cancer surgery and for our research plans for the future.

Gunnar Endin, **Beryl Godley** and **Maud Marsden**, for your kind help with linguistic problems.

The staff of PLOP, for creating the best operating unit at the Karolinska, and for your understanding when I could not be present due to my research.

All the staff of the plastic surgery ward E13, the burn unit F42 and the outpatient clinic, for all your sincere support.

All my colleagues at the Department of Reconstructive Surgery, for creating such a friendly and competent working atmosphere.

All my former colleagues at the Departments of Surgery at Falu and Mora Hospital, for friendship and for schooling me in general surgery.

My mother, Margareta Lagergren, who recently left us, for bringing me up and giving me everything I needed in life. I miss you endlessly.

Sonja, my graceful and beloved wife, for always standing by my side, in happy times and sad, and for being the most important support in my life.

David, my handsome eldest son, for being a wonderful boy and my closest friend.

Jonatan, my lovely younger son, for being such a joy and my true partisan.

My brothers, Jonas och **Jesper**, for being so close and always dependable.

My parents-in-law, Ingegärd and **Hans**, for always being welcoming and taking such an active interest in me and my family.

Manuela Wiesler, world-famous flute-player who recently died, for being my close friend to whom I could confide in all matters, the most intelligent and broad-minded person I have ever met.

All other dear friends, **Anders** and **Carolina**, **David**, **Christer**, **Håkan**, **Mats**, **Stefan**, **Torleif**, **Sten**, **Ingrid**, and the late **Sven Karpe** for all fun and all experiences we have shared.

All friends in **Dalarnas Kammarorkester**, for all relaxing and joyful moments and for all wonderful music we have created together.

All patients, for taking your valuable time to participate in the studies and for making this profession the best you can practise.

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