From the Department of Molecular Medicine and Surgery, Karolinska Institutet,
Karolinska University Hospital Solna, Stockholm, Sweden.

Nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants in breast cancer.

Kristinn P. Benediktsson, M.D.

Karolinska Institutet

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Department of Molecular Medicine and Surgery, Karolinska University Hospital Solna,
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To the memory of my daughters,
Elín Ísabel and Mirra Blær
For the time I wish I had spent with you

CONTENTS

ABSTRACT

Introduction: The surgical treatment of breast cancer has changed rapidly since Halsted´s operation was generally abandoned about 50 years ago. In the 1970s partial mastectomy (PM), followed by radiotherapy (RT), was proven to be oncologically safe for smaller cancer tumours that are not multifocal. For others, approximately 40% of breast cancer patients, modified radical mastectomy (MRM) is the most usual operation, often followed by a reconstruction with autogeneous tissues or implants and in combination with tissue expansion. During the past decade, skin-sparing mastectomy has become a standard operation in many places, but sparing of the nipple-areola complex (NAC) is still a very controversial issue. When this trial started in 1988 very few patients were offered any form of reconstruction after MRM.
Aim: To evaluate nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants (NSM) for patients with breast cancer not suitable for PM.
Patients and methods: During six years 272 patients with breast cancer not suitable for PM were operated on with NSM, and the present papers report results from five trials on those concerning sensibility in the breast (*Paper I*, 80 patients), circulation in the breast (*Paper II*, 43 patients), the rate of capsular contracture (CC) in patients with subcutaneously placed saline-filled implants with textured surfaces (*Paper III*, 107 patients), the CC-rate around MistiGold II® hydrogel-filled implants (*Paper IV*, 41 patients) and survival, rate of locoregional recurrences (LRR) and the outcome after (first event) LRR (*Paper V*, 216 patients) as well as the effect of radiotherapy (RT) on these factors (all papers). The operation was performed through a submammary incision in the majority of cases (217 patients). A biopsy for frozen section was taken from underneath the nipple, which was removed only in cases of malignancy in this. 40% of the patients had lymph node metastases; 12% had cancer *in situ*, 88% invasive cancer. 22% received RT postoperatively, 25% chemotherapy and 57% hormone therapy. At least one year postoperatively, skin sensibilty was measured with von Frey´s monofilaments, circulation with laser Doppler fluxmetry and fluorescein flowmetry, and CC was measured by the Baker/Palmer classification and applanation tonometry under five years postoperatively. Median follow-up in the survival study was 13 years.
Results: Normal (<3.2 milliNewton) or subnormal sensibility was found in the operated breast outside the areola, subnormal on the areola outside the nipple. One third of the patients had normal sensibility in the nipple while 14% lacked sensibility. No reduction was found in skin circulation, whether RT was given or not. The CC-rate was 20.6%, significantly higher for irradiated breasts than for non-irradiated ones, 41.7 and 14.5%, respectively, but a single reoperation with capsulotomy gave very good long-term results. All of the Misti Gold II® implants had to be removed because of CC and increase in volume (up to 50%). Disease-free survival (DFS) was 51.3%, overall survival 76.4% (OS) and the rate of LRR 24.1% (after median 13 years). DFS and OS but not LRR were significantly affected by lymph node status.The survival rates compare well with reported results after MRM in other trials. In irradiated patients the rate of LRR was 8.5%. Survival after LRR was slightly better than has been reported after MRM. The specificity at frozen section was 98.5%. At the end of follow-up 85% of the patients had their nipple-areola complexes intact.
Conclusions: NSM is an oncologically safe procedure in breast cancer given that frozen section excludes malignancy in a biopsy from underneath the nipple. It results in naturally looking breasts with very satisfactory skin circulation and sensitivity, and the rate of CC is acceptable. Misti Gold II® hydrogel-filled implants are not suitable for this procedure. Radiotherapy dramatically reduces the rate of LRR and increases the rate of CC but does not affect superficial skin circulation.

LIST OF PUBLICATIONS

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

I. ***Benediktsson K, Perbeck L, Geigant E, Solders G.***
Touch sensibility in the breast after subcutaneous mastectomy and immediate reconstruction with prosthesis.
Br J Plast Surg 1997, ***50****:443-449.*

II. ***Benediktsson K, Perbeck L****.*
The influence of radiotherapy on skin circulation of the breast after subcutaneous mastectomy and immediate reconstruction.
Br J Plast Surg, 1999; ***52****:360-4.*

III. ***Benediktsson K, Perbeck L.***
Capsular contracture around saline-filled and textured subcutaneously-placed implants in irradiated and non-irradiated breast cancer patients: five years of monitoring of a prospective trial.
J Plast Reconstr Aesthet Surg 2006; ***42(5):****617-20.*

IV. ***Benediktsson K, Perbeck L****.*
Fluid retention in Bioplasty Misti Gold II breast prostheses with development of capsular contracture.
Scand J Plast Reconstr Hand Surg, 2000; ***34****: 65-70.*

V. ***Benediktsson K, Perbeck L.***
Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with a prosthesis: A prospective trial with 13 years follow-up in 216 patients.
Submitted 03/11 2007 to Eur J Surg Oncol.

ABBREVIATIONS

NSM Nipple-sparing subcutaneous mastectomy and immediatereconstruction with implants
SSM Skin-sparing mastectomy
SRM Subcutaneous reduction mammaplasty
NAC Nipple-areola complex
MRM Modified radical mastectomy
PM Partial mastectomy
SNB Sentinel node biopsy
RT Radiotherapy
CMF Chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil
HT Hormone therapy (mostly with tamoxifen)
TRAM Transverse rectus abdominis musculocutaneous
DIEP Deep inferior epigastric perforator
LRR Locoregional recurrence
LDF Laser Doppler fluxmetry
FF Fluorescein flowmetry
CC Capsular contracture
ATQ Applanation tonometry quote
DM Distant metastasis
OS Overall survival
DFS Disease-free survival
ER Oestrogen receptor status (measured as fmol/µg DNA)

ABSTRACT IN SWEDISH
Kort sammanfattning på svenska

Kirurgisk behandling av bröstcancer förekom knappast innan införandet av anestesi på mitten av 1800-talet. Därefter praktiserades det i nästan 100 år en mycket aggressiv operationsmetod (radikal mastektomi ad modum Halsted) medtagande underliggande muskulatur, vilket gjorde armen på samma sida nästan oanvändbar. På mitten av 1900-talet började man att endast ta bort själva bröstet (modifierad radikal mastektomi, MRM) och på 1970-talet visade studier att frånsett när det gäller de största tumörerna eller de som är multifokala går det lika bra att ta bort enbart den sjuka bröstdelen (partial mastektomi, PM) under förutsättning att strålbehandling (RT) ges efteråt till det opererade bröstet. När vår studie startade i december 1988 opererades redan i Sverige ungefär 60 % av bröstcancerpatienter med PM. Hos resten gjordes MRM och endast fåtal av dessa fick chansen till en senrekonstruktion, oftast med s.k. TRAM-lambåer, där stora delar av rectus abdominis-musklerna flyttades upp på bröstet tillsammans med överliggande hud. I England, däremot, hade man redan 1984 börjat med studier på subkutan mastektomi för denna kategori av patienter, och dessa hade visat samma överlevnadssiffror och samma frekvens av locoregionala recidiv (LRR) som efter MRM. Samtidigt visade de första resultaten från studier jämförande PM med och utan RT samma överlevnad hos båda grupperna trots att LRR var mycket vanligare hos dem som inte blivit strålbehandlade. Vi bestämde oss därför för att utvärdera denna metod här i Sverige.
Patienter och metoder. Under knappt 6 år opererades 272 patienter med bröstcancer olämplig för PM med bröstvårtbesparande subkutan mastektomi och direktrekonstruktion med proteser (NSM). Patienterna fick efter noggrann information välja mellan MRM och NSM och merparten valde det senare alternativet. Hos 17 patienter användes s.k. lazy-S snittföring (ovanför och lateralt om bröstvårtgården med submuskulär placering av protesen, grupp A), hos 14 patienter (grupp B) gjordes subkutan reduktionsplastik med submuskulär placering av protesen (SRM). Hos resten av patienterna placerades protesen subkutant med lazy-S snittföring hos 24 patienter (grupp C) och snitt i submammarfåran hos 219 patienter (grupp D). Silikonproteser användes för submuskulär placering medan koksaltproteser för subkutan placering frånsett 22 patienter där hydrogelfyllda proteser av typen MistiGold II® användes (delarbete IV). Biopsi togs alltid för fryssnitt från området precis under bröstvårtan som avlägsnades om det fanns maligna förändringar i denna. Adjuvant behandling gavs i samråd med onkologer från Radiumhemmet och efter samma principer som då gällde för patienter opererade med MRM. 40 % av patienterna hade lymfkörtelmetastaser, 12 % hade endast cancer *in situ* men 88 % invasiv cancer. 22 % fick RT postoperativt, 25 % cellgift och 57 % hormonterapi. Vi har sedan följt dessa patienter i 17 år eller så länge de har levat (median 13 år). En stor del av dem (216) ingår i sista studien i denna avhandling (arbete V), där vi redovisar resultat på överlevnad och recidivfrekvens samt hur det gick för patienter som fick recidiv. 80 patienter ingår i arbete I där sensibiliteten i brösten mättes minst 1 år postoperativt med von Frey´s instrument, d.v.s. 20 hårstrån av olika tjocklekar. Dessutom testades också tio frivilliga, friska kvinnor för att få fram ”normalvärden” för sensibiliteten i kvinnobröst. Dessa visade sig ligga på mindre än 3.2 milliNewton. Alla mätningar gjordes på nio ställen i båda brösten, därav fyra ställen på bröstvårtgården och ett på själva bröstvårtan. Resultaten analyserades avseende sensibiliteten vid de olika operationsmetodgrupperna (A-D). I delarbete II mättes cirkulationen i de opererade brösten på 43 patienter varav 19 hade blivit strålbehandlade. Undersökningen gjordes minst 1 år efter operation eller strålbehandling på tre ställen i vardera bröst med två metoder, fluorescein flowmetry (FF) som mäter cirkulationen endast helt superficialt och laser Doppler flowmetry (LDF), som mäter något djupare, åtminstone 1-2 mm. Resultaten jämfördes mellan det friska och det opererade bröstet och mellan strålade och inte strålade patienter. I delarbete III ingick 107 patienter som alla fick

koksaltproteser med texturerad yta placerade subkutant och varav 24 fick RT postoperativt. Två olika typer av koksaltproteser användes med olika porstorlekar på den texturerade ytan. Patienterna följdes sedan i fem år och undersöktes var tredje månad med två metoder för att mäta kapselkontraktur (CC): Baker/Palmer klassifikation och applanationstonometry. I delarbete IV blev en ny typ av protes, Misti Gold II® (fylld med hydrogel) utvärderad hos 20 patienter och utvecklingen av CC jämförd med densamma hos 20 patienter som erhöll koksaltfyllda proteser. Alla patienterna i detta arbete fick protesen placerad subkutant.
Resultat: *Sensibiliteten* var normal eller nästan normal utanför bröstvårtgården hos alla patienterna men något nedsatt hos de flesta innanför denna och starkt nedsatt på själva bröstvårtan. Dock hade 31 % av patienterna normal sensibilitet i bröstvårtan. Bäst sensibilitet fanns hos grupp B och sämst hos grupp D men skillnaderna var inte väsentliga. Normal *hudcirculation* uppmättes i alla brösten oavsett om strålbehandling gavs eller ej. *Kapselkontraktur* utvecklades hos 20.6 % av patienterna. Frekvensen var 14.5% hos dem som inte fick RT men 41.7% hos strålade patienter (p=0.01). När kapselkontraktur utvecklades blev patienterna reopererade med öppen kapsulotomi som gav mycket bra långtidsresultat. Kapselkontraktur utvecklades hos alla 20 patienterna som fick *Misti Gold II®* proteser. Dessa ökade snabbt i volym, sannolikt p.g.a. osmos, och fick bytas ut mot koksaltproteser. Ö*verlevnadsstudien* (arbete V) visade efter 13 års median uppföljning sjukdomsfri överlevnad (DFS) 51.3%, allmän överlevnad (OS) 24.1% och LRR 24.1%. Dessa överlevnadssiffror är väl jämförbara med det som har rapporterats efter MRM. Hos strålbehandlade patienter var LRR 8.5%. DFS och OS men inte LRR påverkades av lymfkörtelstatus. Överlevnad efter LRR som första händelse var något bättre än det som har rapporterats efter MRM. Specificitet vid fryssnitt var 98.5%. Vid slutet av uppföljningstiden hade 85% av patienterna fått behålla sin bröstvårta.
Slutsatser: NSM är onkologiskt säker när fryssnitt utesluter malignitet i området under bröstvårtan. Efter operationen är det god cirkulation i hela det opererade bröstet och god sensibilitet utanför bröstvårtgården men oftast väsentligen nedsatt innanför den samma. Frekvensen CC är acceptabel, men Misti Gold II® proteser kan inte användas, åtminstone inte med subkutan placering. Postoperativ RT påverkar inte circulationen men resulterar i betydligt reducerad frekvens LRR och ökad frekvens CC.

INTRODUCTION

A very short history of the treatment of breast cancer

Although breast cancer has been with us for at least 4.000 years, the history of its treatment is much shorter. “Bulging tumours of the breast” were reported in a papyrus discovered in Egypt in 1862 (the Edwin Smith papyrus), and the author of the papyrus concluded that there was no treatment for breast cancer [1]. This papyrus has been dated to the 17th century BC but is actually believed to be a transcript of an original papyrus from about 3.000 BC that was probably written by Imhotep, who was a very powerful man in Ancient Egypt, physician to the pharaoh and the architect of pyramids, and later proclaimed as a god. Through the ages there are sporadic accounts in the literature of surgical treatment of breast cancer, such as cutting off the breast completely and pouring boiling oil into the wound, and later cutting and cauterization, all without any form of anaesthesia, of course. However, until the middle of the 19th century AD, the general opinion seems to have been that breast cancer was best left untreated. The early Egyptians probably saw it as a punishment endorsed by the gods, a view shared by many in the middle ages in Europe under the influence of the Roman Catholic church, and in Ancient Greece Hippocrates (460-377 BC) explained it with his humor theory of four bodily fluids (black and yellow bile, blood and phlegm) [2]. His fellow countryman, Caudius Galen (c. 129-200 AD), although performing both eye- and brain surgery, did not consider breast cancer surgery worth while, unless perhaps in its initial stages [3]. He took the view that breast cancer was a systemic disease and that local treatment was therefore not very helpful. Even if he blamed it on melancholia (deep depression), one could argue that time has proved him right regarding the nature of the disease! Anyway, he became very influential by moving to Rome and becoming physician to the Roman emperor Marcus Aurelius. Through centuries to come, his doctrines were to dominate not only the treatment of breast cancer but also that of many other diseases. Even if his views on breast cancer were questioned as early as the 15th century it was not until the introduction of anaesthesia (understandably) in 1846 that real attempts were made in radical breast cancer surgery. A pioneer in the field was Charles Moore (1821-1879) at the Middlesex Hospital in London, but William Stewart Halsted (1852-1922) at the Johns Hopkins Hospital in the USA is generally credited with perfecting this treatment, which was to dominate this field for the next 100 years [4]. He believed that breast cancer was a local disease and that the best treatment was therefore to remove not only the whole breast, but also the underlying muscles and the axillary lymph nodes. This was a highly mutilating surgery, and although survival rates in breast cancer did improve, the patients were left with big problems in the form of lymhoedema and weakness of the arm on the operated side. Many began to doubt that such extensive surgery was needed. In 1948 modified radical mastectomy (MRM) was introduced by D.H. Patey and W.H. Dyson of the Middlesex Hospital in London [5], and subsequent studies on their patients, and those of others, showed no difference compared with radical mastectomy in terms of recurrence and overall survival. The improvement in quality of life for the patients, however, was obvious to everyone. At about the same time, radiation came into common use for cancer therapy. It soon proved to be very effective as an addition to surgery in breast cancer, thereby minimising the necessary extent of surgical treatment. In addition, chemotherapy and hormone therapy have proved to be effective treatments of breast cancer. In the 1970s many trials by Veronesi and others [6,7] proved that early breast cancer could be treated with the combination of partial mastectomy (PM) and radiotherapy (RT) without affecting rates of recurrence or survival. Veronesi was also a pioneer in sentinel node biopsy (SNB), which he and his team at the European Institute of Oncology in Milan started in 1996 [8], and which has restricted considerably the need for axillary lymph node clearance, and thereby spared a number of patients

the troublesome complication of lymphoedema. With the evolvement of mammography, ultrasound and magnetic resonance imaging, breast cancer is being detected at much earlier stages than before. Today it is generally accepted that only 30-40% of breast cancer tumours need to be treated surgically by some form of total mastectomy. It is a growing opinion that breast cancer is a systemic disease (as Galen proposed 1.900 years ago) and should be treated as such, in team work between surgeons, radiologists, pathologists and oncologists.

BACKGROUND

A short history of breast reconstruction

With the trend for less extensive surgery in breast cancer and improvements in plastic surgery came the idea of reconstructing breasts that had been removed. In Scandinavia it began in the 1980s with late reconstructions, often a year after mastectomy, using abdominal flaps known as TRAM (transverse rectus abdominis musculocutaneous) flaps [9], in which one or both of the rectus abdominis muscles was rotated upwards on its supplying superior epigastric artery and with overlying skin to rebuild the breast. This took multiple operations with follow-up surgery spread over weeks or months. Often the nipple was reconstructed later with transplants from the vulva or inner thigh, or by tattooing. Hernias of the abdomen were quite common after this operation in the beginning but have become rare after the introduction of meshes. A variation of TRAM-flaps are the muscle-sparing DIEP (deep inferior epigastric perforator) [10] and SIEA (superficial inferior epigastric artery) [11] flaps. With the evolvement of microsurgery it has also become possible to use 'free' flaps, i.e. connecting the artery of the muscle to an artery in the axilla. Latissimus dorsi muscle flaps [12] have also become common, sometimes with the addition of implants to obtain more volume. Nowadays these operations are often performed in combination with the removal of the breast, in a procedure known as immediate reconstruction, and the cosmetic results are generally very good, even if the sensibility in the reconstructed breasts has been shown to be poor [13]. In the past decade the wide acceptance of skin-sparing mastectomy (SSM) [14,15] has enabled even better cosmetic results in breast reconstruction, as well as normal sensibility outside the areola. An alternative to autologous breast reconstruction is tissue expansion, which was developed by Becker in1984 [16] and came into common use in the 1990s. Most often the expander-prosthesis is replaced with a permanent prosthesis, but tissue expansion can also be used in combination with autologous tissue breast reconstruction.

Specific background

By the late 1980s PM had become the standard treatment in Sweden for small breast cancer tumours, usually followed by RT to the affected breast. Of the remaining breast cancer patients (approximately 40%), who had too large or multifocal tumours, most were treated with MRM and not offered any kind of breast reconstruction. Only the youngest of those who had no lymph node metastases were offered late reconstruction in the form of TRAM flaps. Expander prostheses were not yet in common use in Scandinavia at the time.
In the meantime, preliminary results from studies on patients who had been treated with PM and randomised between RT or not [17,18] showed no statistically significant difference in overall survival (OS) between the two groups, even though the frequency of locoregional recurrences (LRR) was reduced by about 70% by RT. These results have since been confirmed in a longer follow-up of the same studies [19,20] while others have shown small differences in OS [21].

Thus, scientific evidence strongly suggested that OS in breast cancer, at least after partial mastectomy, was not affected by the frequency of LRR but mainly by the primary tumour´s histology, the occurrence of lymph node metastases and the systemic treatment given. In a study by Hinton et al. published in 1984 [22] MRM was compared with subcutaneous mastectomy and immediate reconstruction with a prosthesis, and no difference, either in survival or in the frequency of LRR, was found. Similar results were obtained in a study by Palmer et al. published in 1992 [23]. Al-Ghazal and Blamey [24] have since demonstrated a good or excellent cosmetic result in 85% and moderate or very good patient satisfaction in 96% of their patients after this operation which can easily be performed as a single procedure lasting less than two hours, even including axillary clearance. This caught the attention of my tutor, Leif Perbeck, and seemed to him a promising alternative. Besides, in our opinion it could be offered to almost all women with large and/or multifocal tumours, irrespective of age or lymph node status. At the time we were stationed at the Huddinge University Hospital in Stockholm. It was at that hospital that we started this prospective, controlled clinical trial in December 1988. At most other hospitals in Sweden, MRM continued to be the only option for patients in the same category. In our hospital, as long as they did not have skin involvement, they were given the choice between nipple-sparing subcutaneous mastectomy and immediate reconstruction with a prosthesis (NSM) and MRM without any form of reconstruction. In practice, most of the patients chose the former alternative after receiving thorough information.

The renaissance of subcutaneous mastectomy

Subcutaneous mastectomy means removal of only the glandular tissue of the breast, leaving behind the skin, areola and nipple. It is by no means a new method as it has been used for at least half a century. Before the 1980s, however, it was almost exclusively used for lobular cancer *in situ* and benign breast diseases such as multiple fibroadenoma. It is still not commonly accepted as a treatment against invasive carcinoma but is widely recommended as prophylactic surgery in cases of significant family history of breast cancer. Since the recruiting of patients was finished for the trials in this thesis in October 1994, skin-sparing mastectomy has been introduced and has become the standard treatment for advanced breast cancer in many hospitals around the world. With this method most of the skin outside the nipple-areola complex is spared, which opens up possibilities for a more natural-looking reconstruction with autologous tissues and/or implants and much better sensibility in the reconstructed breast. During the last six years several studies have been initiated to examine the outcome when the skin-sparing is extended to the nipple-areola complex (NAC) in cases with a negative frozen section from underneath the nipple [25-27]. As pointed out by Petit et al. [25], this is essentially the same operation as subcutaneous mastectomy. They have renamed it nipple-sparing mastectomy, and when their surgical method is compared with ours, no essential differences are found regarding the resection of tissues before the reconstruction.

AIMS OF THE THESIS

The aims of the thesis were to evaluate NSM in breast cancer with special attention given to the following factors.

Touch sensibility in the breast.

The influence of radiotherapy on skin circulation of the breast.

Capsular contracture (CC) around saline-filled and textured subcutaneously-placed implants in irradiated and non-irradiated breast cancer patients and the effect of the pore-size of the implants on the CC-rate.

Compare Bioplasty Misti Gold II® breast implants with saline-filled implants in relation to CC-rate when placed subcutaneously.

Survival and LRR-rate with a median follow-up of 13 years and the outcome in patients suffering LRR as a first event.

PATIENTS

Between December 1988 and October 1994, all patients at the Huddinge University Hospital in Stockholm with breast cancer judged unsuitable for PM and without skin or nipple involvement were offered the choice, after being given thorough information, between MRM and nipple-sparing subcutaneous mastectomy with immediate reconstruction with a prosthesis (NSM). Most of them chose the latter, and in fact we performed very few MRMs during that period. A total of 272 patients underwent NSM during those years. About half of the patients had undergone PM less than 3 months earlier, after which multifocality or residual tumour was highly suspected. The other patients were selected directly for NSM because of a tumour size of >3 cm and/or verified or highly suspected multifocality. All the patients gave their informed consent to the procedure after being offered MRM as an alternative. Included in the preoperative information given to the patients was that the nipple would be spared only if frozen section from the tissues underneath it were negative.

Table 1. Distribution of patients in trials

Papers	No. of patients
I only	4
II only	5
IV only	11
V only	53
I & II	2
I & III	2
I & V	40
II & III	1
II & V	5
III & IV	4
III & V	41
IV & V	9
I & II & III	1
I & II & V	6
I & III & V	16
II & III & V	16
II & IV & V	3
III & IV & V	11
I & II & III & V	8
II & III & IV & V	2
All	**240**

Patients were included in all of the present trials consecutively, as far as possible. Fifty-six of the 272 patients were not included in the survival study (Paper IV) for various reasons (see below). Of those, 32 were not included in any other study either. Table 1 shows how many of the remaining 240 patients participated in each of the five trials. Thus, 73 patients were included in one trial only, 104 in two, 55 in three and ten patients in four of the trials.

The operations were performed by Leif Perbeck and seven other surgeons at our clinic (including the author), all of whom were trained by him.

All five trials were approved by the Ethics Committee of Karolinska Institutet, Huddinge University Hospital. All of the patients and the controls in paper I gave their informed consent to participate in the trials.

PAPER I

The original series consisted of 125 consecutive patients operated at least one year previously, 40 of whom were excluded. Ten patients were excluded because of a new operation on the same breast during the year before the study was initiated, one because she had had her nipple removed and seven because both breasts had been operated on. Seven patients had emigrated, and five had died. A consent form with information about the examination was sent to the remaining 85 patients. Five declined to participate. Thus, 80 patients were examined. Their mean age was 54 years (range 40-80). Forty-five patients (56%) had a scar after a previous lumpectomy when admitted for subcutaneous mastectomy. Axillary dissection was performed on 69 patients (86%) either before or at the NSM. Postoperatively, 17 patients (21%) were given RT and 19 patients (24%) chemotherapy.

On the basis of the operative method, the patients were grouped into four groups, which were named with the same letters as the corresponding operative methods, see description in the

Methods section: Group A (n = 15), Group B (n = 13), Group C (n = 24) and Group D (n = 28). There were no significant differences between the groups for the other treatments given. Ten healthy volunteers from the hospital staff, with a mean age of 38 years (range 26-63) were included as controls.

PAPER II

In 43 patients, mean age 53 years (range 38–73 years), skin circulation was examined after NSM. Saline-filled, textured surface prostheses were placed subcutaneously. Nineteen of the patients received postoperative RT (four after LRR), and in those, skin circulation was studied at a minimum of 1 year after RT. None of the patients had any persistent redness of the skin. Twenty-four patients did not receive RT and were examined at least one year postoperatively.

PAPER III

One hundred and forty-five consecutive patients operated upon between June 1991 and September 1994 and on whom the reconstruction was performed with a subcutaneously-located prosthesis, were originally considered for this study. Excluded from the study were all 12 patients who received secondary RT due to LRR during the 5-year monitoring period, all 12 who died or became too sick for review during the first two years of monitoring, and all 14 who had their prostheses permanently removed because of implant failure (without capsular contracture) before the 2-year follow-up. The remaining 107 patients, mean age 54 years (range 32–75 years), were monitored for five years or until death.

PAPER IV

Forty-one patients, mean age 55 years (range 30–81) were randomised for NSM with a Misti Gold II® prosthesis or a saline-filled prosthesis with a textured surface (Siltex®, Mentor or MicroCell®, McGahn) between October 1993 and May 1994.

PAPER V

Of the 272 patients operated on, 56 were not included in this study for various reasons: 39 had bilateral or recurrent carcinoma, 11 had received hormone therapy or chemotherapy preoperatively, three had a history of some other kind of invasive cancer, two emigrated within three months postoperatively, and one had been breast-feeding right up to the operation. The remaining 216 patients, with a mean age of 52.8 (29-81) years, all had primary, unilateral breast cancer, no other kind of cancer, and had not received any treatment preoperatively. Ninety-three of these patients (43%) had cancer in the right breast and 123 (57%) in the left. In 127 patients (58.8%) the primary tumour (the largest one in cases of multifocality) was localised in the upper, lateral quadrant of the breast, in 35 patients (16.2%) in the upper medial quadrant, and in 25 patients (11.6%) in the central part of the breast (underneath the nipple-areola complex). Only 17 of the primary tumours (7,9%) were localised in the lower lateral and 12 (5.5%) in the lower medial quadrant of the breast.

METHODS

SURGICAL TECHNIQUES (All papers)
Four operation methods were used when performing NSM:

A. Lazy-S shaped horizontal incision (above and lateral to the areola) and a submuscularly located prosthesis.

B. Subcutaneous reduction mammaplasty (SRM) through a keyhole skin incision with a wide vertical pedicle of skin and fat and a submuscularly located prosthesis, and a reduction mammaplasty or mastopexy of the contralateral breast.

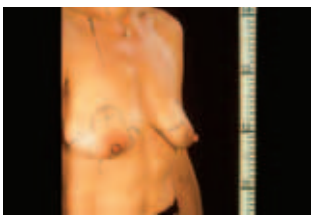


Figure 1c

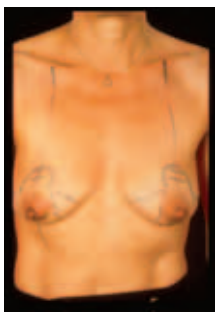


Figure 1a

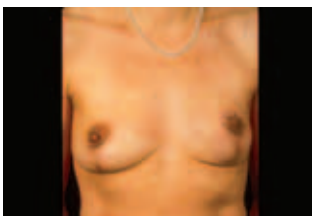


Figure 1b

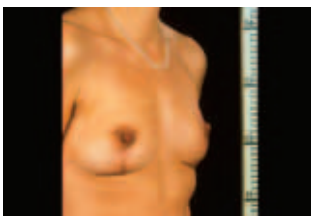


Figure 1d

42 year old woman with multifocal ductal carcinoma in her left breast, operated on with method B. Images preoperatively (Figures 1a & 1c) **and one year postoperatively** (Figures 1b & 1d)**.**

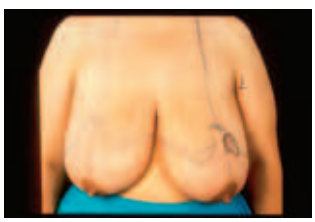


Figure 2a

43 year old woman with a 3.5 cm large cancer in her left breast and macromastia, operated on with method B. Images preoperatively (Figure 2a) **and one year postoperatively**(Figure 2b)**.**

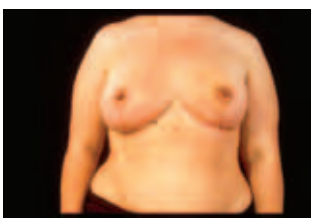


Figure 2b

C. Lazy-S incision and a subcutaneously located prosthesis.

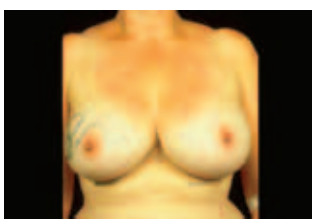


Figure 3a

45 year old woman with a 5 cm large cancer laterally in her right breast and metastases in 2 of 10 lymph nodes, operated on with method C. Images preoperatively (Figure 3a)**and one year postoperatively** (3b)**.**

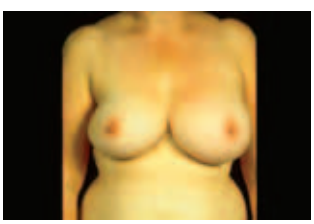


Figure 3b

D. Inframammary incision (15 mm above the submammary fold) and a subcutaneously located prosthesis.

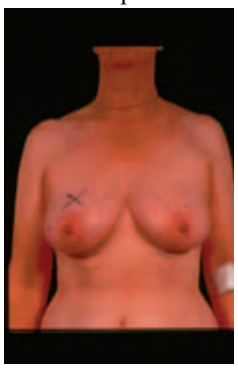


Figure 4a

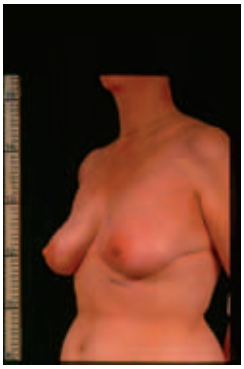


Figure 4c

Figure 4d

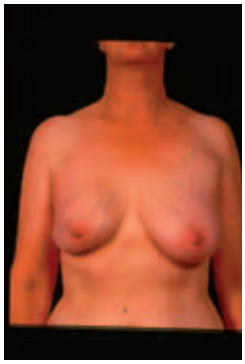


Figure 4b

Figures 4-5 show results after operation with method D.

***Left and above*: 57 year old woman with multifocal cancer in her right breast, preoperatively (Figures 4a and 4c) and 6 months postoperatively (4b and 4d).**

***Right and below*: 57 year old woman initially operated on with PM and axillary clearance because of multifocal cancer in the lateral superior quadrant of her right breast, pre-operatively (5a and 5c) and postoperativelty (5b and 5d). The submammary fold is demonstrated in Figures 5c and 5d.**

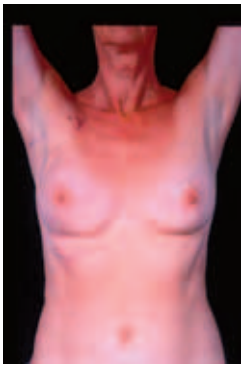


Figure 5c

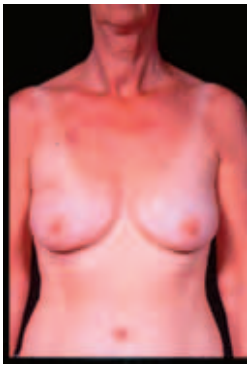


Figure 5a

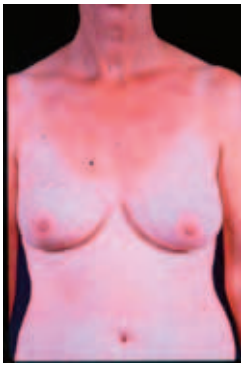


Figure 5b

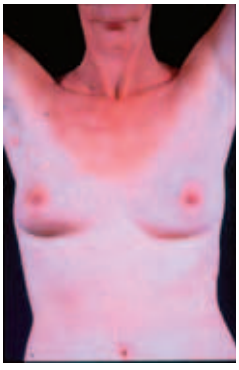


Figure 5d

Method D was used in the majority of cases, 217 patients, method A in 17 cases, method B in 14 and method C in 24 cases. Silicone gel implants were used for method A and B and hydrogel

implants in 22 patients operated on with method D. In the remaining 219 patients we used saline-filled, textured prostheses, most often located subcutaneously, which gives better cosmetic results in ptotic breasts. The subcutaneous tissue was dissected along Scarpa´s fascia. Care was taken to leave behind as much as possible of the subcutaneous fat tissue without endangering the removal of all breast gland tissue. The skin over the tumour was only removed if the two of them could not easily be separated. A 5 mm thick plate of gland tissue with a 20 mm diameter was left beneath the nipple to preserve the blood supply to the areola. A biopsy specimen was taken from the gland tissue immediately adjacent to that plate and sent for frozen section. The resection was continued while waiting for the result of frozen section to minimise the operating time. The gland was undermined off the pectoralis muscle, often with removal of its fascia as well, care being taken to ligate or coagulate the perforator vessels. Axillary clearance was performed through a separate incision. The nipple-areola complex (NAC) was preserved only when no malignant cells were identified in the frozen section. In methods A and B a pocket was created beneath the pectoralis major muscle, laterally under the serratus anterior muscle and distally 1.5 cm below the submammary fold.
In method B the dissection started with the deepithelialization of a vertical pedicle. In the beginning we used a caudal pedicle but later changed to a cranial one, after our measurements of the circulation in the NAC showed a blood flow of 13 % of the normal when a vertical caudal pedicle was used [28].
Sterile sizers were used to estimate the suitable size and shape of the implant. The apprehension was done with the patient in both a horizontal and a sitting position.
A drain was placed both in the axilla and in the breast. The breast drain was kept until the daily volume was 40 ml or less but never longer than eight days. Prophylactic antibiotics were administered during the induction of anaesthesia and continued until a week after rhe removal of the drain.

ADJUVANT THERAPY (All papers)

Adjuvant therapy was given in consensus with the oncologists of Radiumhemmet at the Karolinska University Hospital in Stockholm and following the same policy as for patients undergoing total mastectomy during the same period at our and other hospitals in Stockholm: RT for postmenopausal women with one or more positive lymph nodes and for premenopausal women with four or more positive lymph nodes; chemotherapy (most often six cycles of cyclophosphamide, methotrexate and 5-fluorouracil, hereafter referred to as CMF) for premenopausal women with one or more positive lymph nodes or a very large (≥5 cm) tumour; hormone therapy (mostly tamoxifen 20 mg daily for 2 years, hereafter referred to as HT) in cases of oestrogen receptor (ER) positivity for most of the postmenopausal women and some of the premenopausal ones. ER positivity was defined as >0.04 fmol/μg DNA.

Radiotherapy (All papers)

RT was given locally to the affected breast and ipsilateral lymph nodes (axillary, supraclavicular and parasternal) with tangential, opposite photon beams combined with frontal electron beams (for the lymph nodes) in a total dose of 46 Gy given as 2 Gy fractions five days a week. The energy used was 4-6 mV. No booster dose was given.

ASSESSMENT OF CAPSULAR CONTRACTURE (Papers II, III and IV)

Two methods were routinely used for measuring capsular contracture (CC):

1) Baker's classification modified by Palmer [23]

B 1A. Ideal. Soft breast, looks natural, implant not detectable.
B 1B. Good. Implant palpable, visible in supine position, no distortion.
B 2. Satisfactory. Capsule obvious but not firm; no complaints or distortion.
B 3. Inferior. Capsule firm; minimal distortion, uncomfortable.
B 4. Poor. Capsule firm to hard, looks and feels abnormal; painful.

Baker 3 and 4 are not acceptable and necessitate reoperation.

2) Gylbert´s applanation tonometry [29]
Breast compressibility was evaluated by means of a transparent plexiglass disk with a radius of 10 cm and weighing 302 g. Engraved upon the disk were concentric circles every 10 mm and four symmetrical diameter markers graded in millimetres. The measurements were done with the patient in the supine position, and the disk was placed horizontally on the breast with its centre somewhat medial to the nipple. In patients with soft breasts that slipped laterally the breast was pushed medially in a longitudinal plane to the lateral border of the thoracic wall. The disk was moistened with alcohol to facilitate the evaluation of the imprint area. A longitudinal diameter and a transverse diameter perpendicular to each other were measured. It has been shown that the form of the imprint of the disk can be approximated by the form of an ellipse. The imprint area A, with axes a and b, was calculated according to the formula: $A = \pi\ a\ b/4$. Since the disk gives rise to a constant compression force, the counter-pressure from the breast is inversely proportional to the contact area between the disk and the breast. Changes in softness of the breast from one measurement to another could, therefore, be calculated and compared in the same patient. The relative breast compressibility was defined as the ratio of the imprint area measured during the follow-up period and the initial imprint area measured at the end of the operation. A ratio (hereafter named applanation tonometry quote, ATQ) lower than 0.5 was regarded as highly indicative of CC.

PAPER I

Assessment of touch sensibility thresholds
Nine of the controls were tested twice with an interval of 6-12 months to evaluate the reproducibility of the test. For analysis of the results each control's right breast served as the "treated" one and the left breast as the contralateral one. Besides the ten healthy controls, the patient's "healthy" breast (the untreated side) served as control in each case.
Tactile thresholds were assessed with von Frey's hairs (Figure 6a). With the patient in a semisupine position with closed eyes in a warm room (23° C), a series of 20 nylon filaments (Stoelting Co., Wood Dale, IL, USA) with bending thresholds of 0.035-2052 milliNewton (mN) (0.0036-209.2 g) were applied perpendicularly to the skin at nine positions on each breast (Figure 6b) : on the nipple (test site 3), at 9, 3, 12 and 6 o'clock just inside the areola (sites 2, 4, 7 and 8 respectively) and at four corresponding sites 1.5-2.5 cm outside the areolar edge, depending on breast size (sites 1, 5, 6 and 9 respectively). The threshold was defined as the minimal bending force (in mN) of the thinnest filament sensed by the subject in a descending

series of applications (‘no value’) in four trials. When none of the filaments was sensed the sensibility was registered as 2000 mN.
All 20 filaments were calibrated exclusively for this study on a microscopic balance. The values of the mass in grams required to bend the tip of the filament were converted to force units (mN) by the formula F = m x g (g = 9.818).
The following were done to minimise errors:

1. The same instrument was used for all measurements after calibrating its filaments on a microbalance.
2. The same investigator performed all the measurements in the same surroundings and at the same room temperature and took care to apply the filaments in the same way every time.

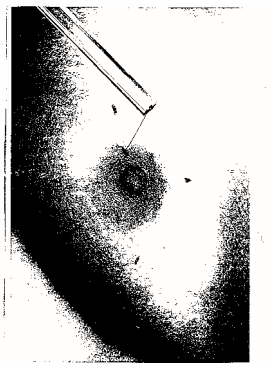


Figure 6a
Measuring of sensibility with von Frey´s instrument at test point 7 in right breast.

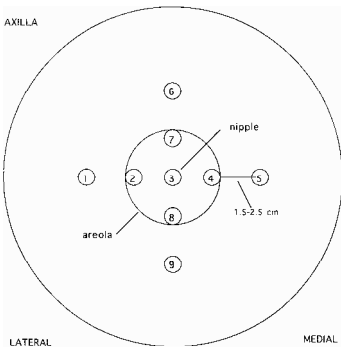


Figure 6b
All nine test points on right breast.

Statistical methods

Values for touch thresholds are given in mN as medians and interquartile range. Because of skewness
of the data from the breast cancer subjects all results were log-transformed and then analysed according to a factorial experiment analysis of variance with one independent factor and two dependent factors. The independent factor was group (operative method) with five levels (A-D and controls), and the dependent factors were side with two levels (treated and untreated breast) and test site with nine levels. In case of significant interactions between the factors in the model, simple main effects were examined with multiple comparisons test according to Bonferroni/Dunn. $P < 0.05$ was accepted as significant.

PAPER II

Calculation of skin circulation with laser Doppler fluxmetry

A laser Doppler fluxmetry (LDF) with a differential detection system (Periflux Pf 1 c, Perimed AB Järfälla, Sweden) was used for the measurements. The operating principle of LDF is that monochromatic laser light is broadened spectrally by moving objects such as blood cells, whereas light beams scattered in static structures alone remain unchanged in frequency. The

flowmeter output signal, measured in volts, is proportional to the number of blood cells multiplied by their average velocity within the scattering volume. In our experiment we used a system with a filter of 4 kHz, a time constant of 1.5 s and gain x 10. The results are expressed in volts. The Pf 108 probe using a specially made adapter with a concave indentation for the nipple was used in order to stabilise its pressure on and movements over the tissue. The probe was held manually.

Calculation of skin circulation with fluorescein flowmetry

The technique of fluorescein flowmetry (FF) has been described in detail elsewhere [30] and is therefore only summarised here. The skin circulation (or rather the transcapillary exchange of sodium fluorescein in the skin) is expressed as a fluorescence index, which is the ratio between the fluorescence obtained during the first circulatory passage of sodium fluorescein and the rise time, defined as the time interval between the occurrence of 10 % and 90 % of the maximum fluorescence. The maximum fluorescence reflects the fraction of cardiac output distributed to the tissue according to Sapirstein's indicator fractionation principle [31]. The rise time indicates the time taken for 80 % of the bolus to disperse, and the use of this factor thus eliminates the uncertainty as to when the first and the last part of the bolus become trapped in the tissue. Rise time is an expression of blood velocity. It has been shown to correlate both with the mean transversal time of the bolus proper (r=0.96) and the mean transit time of the system (r=0.74) [30]. Rise time is inversely proportional to cardiac output, but is also influenced by peripheral resistance. Since the amount of sodium fluorescein administered is known, groups of subjects can be compared.

Photographic equipment and techniques used in evaluation of the images

A Nikon F 501 (yellow Barrier: Scott glass GG 495 or Kodak gelatine Wratten filter 15) with a Paffrath & Kremper ringflash (blue excitation filer: Kodak gelatine Wratten filter 47 A) was used. Values were expressed in density units, with the background density from the tissue fluorescence subtracted.

Statistical analysis

Analysis of variance showed a fairly normal distribution of values in all positions on both breasts as measured with LDF but considerable skewness as measured with fluorescein flowmetry. All data are therefore expressed as medians and interquartile ranges. Statistical hypotheses were tested by a two-tailed Wilcoxon matched-pairs sign ranks test and corroborated by a multiple comparison test as described by Bonferroni/Dunn where the dependent factor was position with three levels. When comparing treated side with untreated side, two dependent factors were used; position with three levels and side with two levels. A P value of less than 0.05 was accepted as significant.

PAPER III

The first 20 patients received Siltex® prostheses from Mentor. Thereafter, however, two types of round prostheses with different pore sizes, but otherwise comparable, were randomly chosen. These were Siltex®, with an average pore diameter of 33 mm and an average pore depth of 27 mm, and Microcell® from McGahn with an average pore diameter of 400 mm and an average

pore depth of 150 mm. All implants were placed subcutaneously. Twenty-four patients received RT postoperatively.
The first applanation tonometry examination was done when the patient was on the operation table before a dressing was applied, and further measurements (combined with a cosmetic evaluation) were made six weeks, and three, six, nine and 12 months postoperatively. Three surgeons and one registered nurse, all experienced (one on each occasion), randomly examined the patients postoperatively, evaluated them using Baker's classification, and did the applanation tonometry. A systematic difference in the cosmetic evaluation between different examiners was ruled out by comparing the evaluations at nine and 12 months.

Statistical analysis

Data are expressed as mean or median. Statistical hypotheses were tested by Student's test for unpaired data or by the difference test for two proportions, and a p-value of less than 0.05 was accepted as significant. Statistica (version 7) was used for the analyses.

PAPER IV

The Misti Gold II® (Bioplasty, The Netherlands) breast implant was introduced in 1987. It has a textured surface and is pre-filled with viscous polyvinyl-pirrolidone (PVP)-hydrogel, which gives excellent results in terms of comfort. Twenty patients were given 22 Misti Gold II® prostheses (two patients bilaterally), with a median volume of 210 ml (range 140–240), and 21 patients were given saline-filled prostheses (one patient bilaterally), of whom 11 patients were given Siltex® with a median volume of 175 ml (range 125–285) and ten MicroCell® with a median volume of 190 ml (range 75–210), all placed subcutaneously. Seven of the patients with the Misti Gold II® implants and five of those with saline-filled implants received RT postoperatively. The CC-rate was evaluated after 12 months or when the patient was reoperated on for CC. To detect even a low degree of CC the discrimination level for CC was set at ATQ 0.75 and B2 (not B3 which is the usual level). The change in volume of the removed Misti Gold II® implants was measured in the last 12 patients.

Statistical analysis

The significance of differences between groups was assessed using Fisher's exact test. The increases in volume of the prostheses were expressed as median (range), and the significances assessed by the Wilcoxon pair sign rank test. Probabilities of less than 0.05 were accepted as significant.

PAPER V

Axillary clearance was performed in all patients with invasive carcinoma and in all except 15 of the patients with cancer *in situ*. The number of removed lymph nodes varied from four to 20 (mean 8.8). Eighty-seven patients (40.3%) had metastases in 1-20 (mean 2.3) lymph nodes. The staging of the patients is shown in Table 1.
ER was measured in the tumours whenever possible. Some of the tumours were too small to obtain ER, and it was not measured for cancer *in situ*.

The use of adjuvant therapy is described below and summarised in Table 2. RT was given, within a year postoperatively, to 47 patients (21.8%), CMF to 53 (24.5%) and HT to 122 (56.5%). Sixty-six patients (30.6%) received no adjuvant therapy.
All patients were monitored at our clinic, at least every 3 months for the first 5 years, and thereafter at least once a year. The date of the last assessment was May 26th, 2006.
To facilitate the detection of recurrences we used mammography, slightly modified because of the presence of implants, ultrasound and magnetic resonance imaging [32].

Statistical analysis

Data are expressed as mean or median. Statistical hypotheses were tested by Student's test for unpaired data or by the difference test for two proportions, and an estimated two-tailed p value of less than 0.05 was accepted as significant. The primary end-point was survival. The definition of locoregional recurrence was failure in the ipsilateral breast, axilla or supra/infraclavicular fossa as a first event. Tumours with a different location and/or histopathology from that of the primary tumour were also recorded as recurrences. Distant metastases are also reported as first site of failure, even when locoregional recurrence was detected simultaneously. Disease-free survival and overall (breast cancer-specific) survival were estimated by the Kaplan-Meier method. Indications for censoring were the occurrence of contralateral breast cancer, any other type of cancer, death by other causes than breast cancer, or emigration (2 patients). The log-rank test was used to compare different groups. Statistica (version 7) was used for all analyses.

RESULTS

PAPER I

In the healthy controls we found an even distribution of threshold values and no significant differences between sides. The mean values for the right and left side were therefore used for calculation of normal limits. Based on the data from the controls, threshold values < 3.2 mN were considered as normal, 3.2-20 mN as moderately raised and 20.1-200 mN as highly raised. Values exceeding 200 mN were judged to represent loss of touch sensation.

In all four patient groups the touch threshold values on the treated breast were generally high and unevenly distributed on the NAC (sites 2, 3, 4, 7 and 8), but much lower and more evenly distributed outside the areola (sites 1, 5, 6 and 9), where the highest median touch thresholds were found laterally and inferiorly (sites 1 and 9; range 2.5-l 1.6 mN) and the lowest ones ($P < 0.001$ compared to any other site in groups A-D together) medially (site 5; range 1.5-1.8 mN). Median values for different test sites in the different groups are given in Table 2. Patient groups A, C and D showed significantly higher touch thresholds as compared with the controls on all test sites except site 5 for group A and site 4 for group C. In group B (patients who had undergone SRM) no significant differences were found in touch thresholds as compared with the controls except on site 9 (inferiorly on the skin).

In Graph 1 the means of the medians for all nine test sites in the different groups (Table 2) are compared. When all test sites were combined, there were no significant differences between the results for group A (implant located submuscularly) and group C (subcutaneous location of implant). In the controls the median touch threshold values for all test sites combined were significantly lower than in any of the patient groups except group B. In group B the touch thresholds were generally lower than in the other patient groups, but the difference was significant only in comparison with group D.

The inframammary incision (group D) resulted in slightly more impaired sensibility than the lazy-S incision (group C), but the difference was significant only for sites 4 and 8 (both on the areola) and not for all nine test sites combined.

When the patients who had undergone axillary dissection ($n = 69$) were compared with those who had not ($n = 11$), no differences were found at the NAC, but the threshold values were slightly higher at test sites outside the areola (sites 1, 5, 6 and 9; $p < 0.05$) in the axillary dissection group. Neither RT, CMF nor previous PM affected the results significantly; however, few patients had RT or CMF. No correlation was found with the patients' age or with the interval between operation and examination.

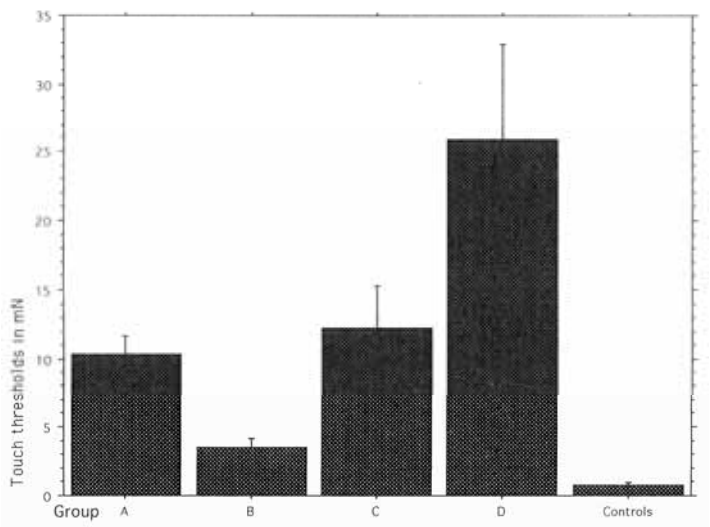
In the contralateral (untreated) breasts the results obtained from all test sites were within our normal limits. Compared to the controls there were no significant differences in touch thresholds for any of the patient groups when all test sites were considered together. Compared to the treated breasts significantly lower touch thresholds were found in the contralateral breasts at all test sites in groups A and D and at all except site 4 in group C, but in group B the differences were significant only for sites 4, 5, 6 and 9.

Table 2. Median touch thresholds on the treated breast and in the controls.

Group	TEST SITES									Mean
	1	2	3	4	5	6	7	8	9	1-9
A	11.6	11.6	9.1	19.8	1.9	9.1	11.6	9.1	9.1	10.3
	(176.4)	(552.9)	(114.8)	(60.5)	(3.4)	(28.4)	(41.7)	(59.9)	(32.8)	
B	2.5	3.5	3.5	3.5	1.8	1.8	9.1	3.5	2.5	3.5
	(7.6)	(8.7)	(1.6)	(11.7)	(1.5)	(3.3)	(17.5)	(9.9)	(21.9)	
C	6.3	19.8	9.1	9.1	1.9	3.5	33.8	19.8	6.3	12.2
	(104.1)	(64.1)	(31.8)	(13.3)	(2.5)	(38.8)	(148.9)	(31.4)	(33.4)	
D	11.6	57.6	33.8	19.8	1.9	2.7	26.8	67.6	11.6	25.9
	(148.9)	(167.8)	(106.2)	(141.1)	(11.5)	(25.6)	(90.1)	(140.3)	(37.2)	
Total	9.1	19.8	9.1	10.4	1.9	3.0	19.8	19.8	9.1	11.3
A-D	(141.1)	(148.4)	(45.4)	(30.8)	(3.0)	(18.0)	61.3)	(64.1)	(31.9)	
Contr.	0.2	0.3	1.2	1.7	0.1	0.2	1.0	1.5	0.6	0.8
	(0.3)	(1.8)	(1.8)	(2.9)	(0.9)	(0.3)	(2.7)	(2.4)	(1.7)	

All values are in milliNewtons. Figures in parentheses are interquartile ranges (IQR = q^3-q^1)

Graph 1. Mean values (bar: standard error) of median touch thresholds for all test sides (1-9) of the treated breast in each patient group (A-D) and in controls.



PAPER II

In the operated breasts both LDF and FF indicated significantly higher circulation at position 2 (the nipple-areola complex) in the irradiated breast than in the non-irradiated breast, but no significant differences at other positions (Tables 3 and 4). When all positions were looked at together (as one compact variable) LDF (but not FF) showed significantly higher circulation in the irradiated group (P = 0.04 and 0.22, respectively). When comparing the ratio operated/non-operated breasts, FF (but not LDF) showed a significantly higher ratio (better circulation in the operated breast) at position 2 in the irradiated group (Table 4). When all positions were looked at together as one compact variable, no differences were found with either method. Neither LDF nor FF showed any differences between operated and non-operated breasts at any of the three positions in either of the two groups. LDF showed that the circulation in the NAC (position 2) was about 2–3 times higher than in positions 1 (P < 0.0001) and 3 (P < 0.0001) both in the irradiated and in the non-irradiated operated breast and also in the contralateral, untreated breast. There was no difference in skin circulation between positions 1 and 3 in either the irradiated, the non-irradiated or contralateral breast.
FF showed no differences in skin circulation between the different positions either in the irradiated, non-irradiated or in the contralateral untreated breast (Table 4).
The frequency of CC measured at the time point for the skin circulation measurement was classified as B 3 in 13% of the non-irradiated breasts needing reoperation and 26% of the irradiated breasts. Corresponding values for B 2 were 16% and 21%, respectively.

Table 3 Skin circulation in three different areas of the breast: 2 cm above the nipple-areola complex (position 1); within the complex (position 2); and 2 cm below the complex (position 3), measured by laser Doppler fluxmetry in the operated, irradiated breast and in the non-operated breast. Numbers are medians (IQR). RT = Irradiated breasts (n = 19), Non RT = non irradiated breasts (n = 24). Laser Doppler fluxmetry (volts)

Position	*1*			*2*			*3*		
	RT	*Non RT*	*P*	*RT*	*Non RT*	*P*	*RT*	*Non RT*	*P*
Operated breast	8.8 (3.9)	6.6. (1.9)	0.07	23.6 (12.1)	18.6 (15.5)	0.04	9.0 (3.7)	6.9 (4.7)	0.93
Non-operated breast	7.4 (6.0)	7.0 (2.8)	0.11	21.2 (7.8)	16.0 (12.0)	0.12	9.2 (3.6)	7.4 (2.5)	0.08
Ratio op./non-op.	1.04 (0.57)	1.01 (0.29)	0.43	1.05 (0.46)	1.06 (0.65)	0.79	0.94 (0.36)	1.03 (0.45)	0.22

Table 4 Skin circulation in three different areas of the breast: 2 cm above the nipple-areola complex (position 1); within the complex (position 2); and 2 cm below the complex (position 3), measured by fluorescein flowmetry in the operated, irradiated breast and in the non-operated. Numbers are medians (IQR). RT = Irradiated breasts (n = 19), non RT = non irradiated breasts (n = 24). Fluorescein flowmetry (Δ density units 10^{-2}/s)

Position	*1*			*2*			*3*		
	RT	*Non RT*	*P*	*RT*	*Non RT*	*P*	*RT*	*Non RT*	*P*
Operated breast	0.10 (0.12)	0.12 (0.15)	0.50	0.13 (0.26)	0.10 (0.13)	0.04	0.14 (0.10)	0.14 (0.13)	0.66
Non-operated breast	0.10 (0.15)	0.17 (0.17)	0.79	0.10 (0.12)	0.10 (0.16)	0.39	0.13 (0.18)	0.17 (0.16)	0.44
Ratio op./non-op.	1.10 (0.50)	1.00 (0.33)	0.21	1.33 (1.74)	1.00 (0.58)	0.02	1.08 (0.47)	1.12 (0.30)	0.13

PAPER III

All 107 patients were monitored for at least 2 years. Thirteen patients died after the 2-year follow-up, while one moved away and six suffered implant failure and did not receive new implants. The remaining 87 patients were monitored for 5 years. The mean monitoring time was 56 months (not counting additional monitoring for reoperated patients), range 24–60, median 60 and standard deviation 9.37.
The rate of CC was significantly higher among patients who had received RT (Tables 5 and 6). The difference was not evident during the first 6 months but was highly significant thereafter, even at 5 years as measured using applanation tonometry, when most of the patients with CC had undergone a corrective operation. Twenty-two patients developed CC, 15 during the first year, three during the second year and four thereafter. Of those who developed CC, 10 had previously received RT, and 12 had not. Six of these patients were not reoperated because of advanced disease or because they chose not to be. The remaining 16 patients were reoperated, one with closed capsulotomy, 15 with open capsulotomy, four during the first year after the primary operation, eight during the second year and four in between the second and sixth year. None of the 16 reoperated patients had a recurrence of CC during the monitoring period of 29–60 months (median 60) after the corrective operation. At the last follow-up after the reoperation, 14 patients measured as Baker 1A, one as Baker 1B and one as Baker 2.

Table 5 Frequency of capsular contracture (B 3 or 4) for different kinds of implants and for irradiated patients compared with non-irradiated

	Microcell®			Siltex®			All		
	R+	*R−*	All	*R+*	*R−*	All	*R+*	*R−*	All
Number	11	34	45	13	49	62	24	83	107
Caps. contr.	6	8	14	4	4	8	10	12	22
% of number	54.5	23.5	31.1	30.8	8.2	12.9	41.7	14.5	20.6
p-values M/S and *R+*/*R−*				.248	.039	.025		.012	

R+, patients who had undergone X-ray therapy; *R−*, patients who had not been treated with X-rays.

Table 6 Baker/Palmer classification of operated breasts 1, 2 and 5 years after primary operation

	1 year			2 years			5 years		
	R+	*R−*	All	*R+*	*R−*	All	*R+*	*R−*	All
Number	24	83	107	24	83	107	19	68	87
Baker classification									
1A	7	52	59	7	55	62	6	42	48
%	29.1	62.7	55.1	29.2	66.3	58.0	31.6	61.8	55.2
1B	6	10	16	3	4	7	0	5	5
%	25.0	12.0	15.0	12.5	4.8	6.5	0.0	7.4	5.8
Classification									
2	4	13	17	6	15	21	6	13	19
%	16.7	15.7	15.9	25.0	18.1	19.6	31.6	19.1	21.8
3-4	7	4	11	3	2	5	1	2	3
%	29.2	4.8	10.3	12.5	2.4	4.7	5.2	2.9	3.4
Reop. caps. contr.	0	4	4	5	7	12	6	6	12
%	0.0	4.8	3.7	20.8	8.4	11.2	31.6	8.8	13.8
p-value *R+*/*R−* (B 3-4 and reop.)	.016			.011			.013		

R+, patients who had undergone X-ray therapy; *R−*, patients who had not been treated with X-rays.

Patients with Microcell® implants seemed to develop CC more often than those with Siltex® implants. The difference was significant ($p<0.05$) between the two types of implants when counting all included patients and among those patients that had not received RT, but not significant among the irradiated patients. There was no difference in the incidence of implant failure (rupture) between the two types of implants. Eleven patients suffered implant failure after the 2-year follow-up, and five of those received new implants. The overall deflation rate in this study was 17.2%.
There was a good correlation between the two methods for evaluation of CC, and there was no change in the contralateral breasts during the monitoring period.

PAPER IV

Two of the MistiGold II® implants and one of the saline-filled implants were removed because of infection. Fourteen of the remaining 20 MistiGold II implants were classified after one year postoperatively as B 2 or 3, compared with five of 20 saline-filled implants ($p = 0.01$). There were no differences in Baker's classification between the two types of saline-filled implants used, so they were analysed together. The ATQ of the breasts measured by applanation tonometry showed in the MistiGold group that 16 of 20 had an ATQ<0.75, compared with 10 of 20 in the saline-filled implant group ($p = 0.096$). In the last 12 MistiGold II® prostheses that were removed due to CC (B 2 or 3) after an interval of 12 to 40 months postoperatively, the volume of the implant was measured. They had all gained in volume, in relation to time by a median of 83 ml (range 30–123) after a median of 24 months (range 13 to 40), giving an increase of 48% (range 22%–55%). All MistiGold II® implants were removed within 40 months, because of of CC.

PAPER V

The definitive histopathological examination showed multifocal tumours in 159 (73.6%) of the treated breasts. Ductal invasive carcinoma was the most common histopathological diagnosis, but 29 patients had cancer *in situ* exclusively, and nine further patients had predominantly cancer *in situ*, but with a small (microscopic) component of invasive carcinoma (Table 7). ER was obtained in all but 64 patients, of whom 29 had cancer *in situ*. It was thus recorded for 152 patients (70.4%) of whom 121 (79.6%) had ER-positive cancer, but the mean ER for all 152 was 0.88 fmol/µg DNA.

The median follow-up time was 13.0 years (mean 11.3, range 0.2-17.5). For patients who were still alive at the last assessment the median follow-up time was 15.0 years. DFS was 51.3% and OS 76.4% (Table 7 and Graph 2 /Figures 1-2)). After 10 years DFS was 60.0% and OS 80.5%. DFS was significantly less favourable in patients with >3 positive lymph nodes at primary surgery than those with no positive lymph nodes ($p<0.05$). OS was significantly dependent on lymph node status, tumour size, staging and ER, partly on histopathology (when comparing cancer *in situ* with invasive cancer), but not on age or on the occurrence of multifocality (Table 7 and Graph 2/Figure 3b).

Fifty-two patients (24.1%) had LRR as a first event (Table 7). The LRR rates at five and ten years were 16.2% and 20.8% respectively. Forty-four patients (20.4%) suffered distant metastases (DM) as a first event or simultaneously with LRR (nine patients). The most usual locations for DM were bone/marrow (54.5%), lung (18.2%), liver (11.4%) and brain (6.8%). The mean time of appearance of LRR was 4.5 years (median 2.9, range 0.5-14.2) and of DM 4.9 years (median 3.6, range 0.2-14.0) after primary surgery. The LRR rate was significantly dependent on age but not on lymph node status, tumour size, ER, histopathology or staging (Table 7). Although ductal cancer tended to recur more often than lobular cancer, the difference was not statistically significant.

DFS, OS and LRR after different kinds of adjuvant therapy are shown in Table 8.

RT dramatically lowered the frequency of LRR, although irradiated patients had a much shorter OS than non-irradiated ones (because of an initially worse prognosis).

Thirty-four of the LRR (65.4%) were located in the same quadrant of the breast as the primary tumour, and four (7.7%) were located outside the breast (three in the axilla, one in the supraclavicular fossa). No recurrence was observed in the muscle layer behind the prosthesis. Nineteen (36.5%) of the LRR were multiple. Forty-four of the LRR (84.6%) showed the same

histology as the primary tumour. Invasive cancer was found in 45 and cancer *in situ* in seven of the LRR. Two of the invasive cancer tumours recurred as cancer *in situ*, and two of the cancer *in situ* tumours recurred as invasive cancer.

Table 7. Survival and locoregional recurrence rate in relation to prognostic factors.

		N(%)	After 5 years			After 10 years			After 13 years (median time)			
			DFS %	OS %	LRR N(%)	DFS %	OS %	LRR N(%)	DFS %	OS %	LRR N(%)	DM N(%)
Age	<50	95(44.0)	62.5	82.8	21(22.1)	56.8	79.3	26(27.4)	49.5	72.2	29(30.5)	16(16.8)
	>49	121(56.0)	71.0	85.0	14(11.6)	62.0	81.5	19(15.7)	52.0	80.5	23(19.0)*	28(23.1)
Stage	0	29(13.5)	82.0	100	5(17.2)	73.0	100	6(20.7)	70.0	100	7(24.1)	1(3.4)
	I	72(33.3)	73.0	91.5	12(16.7)	64.5	87.2	16(22.2)	50.0	83.6	20(27.8)	10(13.9)
	IIA	61(28.2)	71.0	90.0	11(18.0)	64.0	86.0	13(21.3)	55.0	76.7	15(24.6)	11(18.0)
	IIB	21(9.7)	43.0	57.0	3(14.3)	33.0	57.0	5(23.8)	32.3	56.5	5(23.8)	9(42.9)
	IIIA	28(13.0)	55.0	66.8	4(14.3)	48.8	59.0	5(17.9)	48.8	55.0	5(17.9)	9(32.1)
	IIIC	5(2.3)	0.0	20.0	0(0.0)	0.0	20.0	0(0.0)	0.0	20.0	0(0.0)	4(80,0)
Ln	0	129(59.7)	73.0	92.0	23(17.8)	67.5	89.2	28(21.7)	57.0	84.5	34(26.4)	17(13.2)
	1-3	55(25.5)	64.5	80.0	8(14.5)	52.6	76.5	12(21.8)	45.0	74.4	13(23.6)	14(25.5)
	>3	32(14.8)	46.5	58.0	4(12.5)	44.0	51.5	5(15.6)	40.0	47.6*	5(15.6)	13(40.6)*
T(mm)	<21	140(64.8)	76.0	92.8	22(15.7)	68.0	90.0	28(20.0)	57.0	87.2	34(24.3)	18(12.9)
	21-50	73(37.8)	50.0	67.5	12(16.4)	42.0	62.7	16(21.9)	40.5	50.0*	17(23.3)	26(35.6)
	>50	3(1,4)	66.8	66.8	1(33.3)	66.8	66.8	1(33.3)	66.8	66.8	1(33.3)	0(0.0)
ER (fmol/ µg DNA)	<0.05	31(14.4)	41.0	52.6	6(19.4)	41.0	49.0	6(19.4)	41.0	48.7	6(19.4)	13(41.9)
	>0.04	121(56.0)	70.0	86.0	18(14.9)	60.0	82.3	26(21.5)	49.0	74.0*	31(25.6)	26(21.5)*
	Unknown	64(29.6)	76.6	95.0	11(17.2)	69.0	93.5	13(20.3)	63.3	93.5	15(23.4)	5(7.8)
Patho-histology (primary)	Ductal	122(56.5)	62.3	78.0	22(18.0)	54.9	73.5	28(22.9)	42.3	66.5	33(27.0)	30(24.6)
	Lobular	40(15.5)	73.3	84.0	3(7.5)	67.0	82.5	4(10.0)	61.0	78.3	5(12.5)*	10(25.0)
	Mixed	16(7.4)	62.0	87.5	3(18.7)	47.5	82.0	4(25.0)	47.5	81.0	4(25.0)	3(18.8)
	Pred. id.	9(4.2)	78.0	100	2(22.2)	67.0	100	3(33.3)	66.5	100	3(33.3)	0(0.0)
	DCIS	20(9.2)	79.6	100	4(20.0)	73.5	100	5(25.0)	66.5	100	6(30.0)	0(0.0)
	LCIS	9(4.2)	88.8	100	1(11.1)	78.0	100	1(11.1)	78.0	88.0	1(11.1)	1(11.1)
Multi-focality	Yes	159(73.6)	73.0	87.3	23(14.5)	64.0	83.2	29(18.2)	53.0	64.9	35(22.0)	30(18.9)
	No	57(26.4)	54.0	74.8	12(21.0)	48.2	73.0	16(28.1)	45.5	63.6	17(29.8)	14(24.6)
All patients		216	68.0	83.5	35(16.2)	60.0	80.5	45(20.8)	51.3	76.4	52(24.1)	44(20.4)

N = Number of patients. DFS = Disease-free survival; OS = Overall survival; LRR = Locoregional recurrence; DM = Distant metastases; Ln = Lymph node status (number of "positive" lymphnodes at primary operation); T = Tumour size (largest diameter); ER = Oestrogen-receptor status; Pred. id. = Predominantly intraductal. *p<0.05

Outcome in patients who suffered locoregional recurrences

All of the LRR were treated by surgery (six by salvage mastectomy, 46 by local excision), 35 by radiotherapy, seven by chemotherapy and 20 by hormone therapy. Ten patients (19.2%) suffered secondary recurrences, three of these had a third recurrence, and one patient had uncontrollable disease (recurrence after salvage mastectomy). The histopathology of the ten LRR that rerecurred was ductal carcinoma in eight cases and DCIS in two.
The 5-year rate of freedom from subsequent LRR or DM and the rate of OS after LRR as a first event were 60% and 82%, respectively (Graph 2/Figures 4 and 5). The corresponding figures after 10 years were 48.5% and 76.3%, respectively. There was no statistically significant difference in OS (from the date of primary surgery) between patients who suffered LRR as a first event and those who did not (Graph 2/Figure 6). However, OS after primary surgery was significantly worse for patients who suffered an early LRR (< 3 years after primary surgery) than for those who suffered a late LRR (86 % and 68% respectively, p=0.03). OS after the occurrence of LRR was also worse for "early-LRR patients" than for "late-LRR patients", but here the difference was not statistically significant.

Table 8. Survival and locoregional recurrence rate after different kinds of adjuvant therapy.

		N(%)	After 5 years			After 10 years			After 13 years (median time)		
Adjuvant therapy			DFS %	OS %	LRR N(%)	DFS %	OS %	LRR N(%)	DFS %	OS %	LRR N(%)
RT	Yes	47(21.8)	63,5	66,0	2(4,3)	54,0	61,5	4(8,5)	51,5	59,5	4(8,5)
	No	169(78.2)	68,3	88,5	33(19,5)	62,0	85,0	41(24,3)	52,0	80,6*	48(28,4)*
CMF	Yes	53(24.5)	56,0	77,0	10(18,9)	50,0	71,0	13(24,5)	48,0	66,7	14(26,4)
	No	163(75.5)	71,5	85,2	25(15,3)	42,6	85,2	32(19,6)	52,3	78,7*	38(23,3)
HT	Yes	122(56.5)	74,5	82,7	13(10,7)	63,5	78,3	20(16,4)	53,0	72,5	25(20,5)
	No	94(43.5)	60,0	87,3	22(23,4)*	55,5	82,5	25(26,6)	50,0	78,6	27(28,7)
RT+CMF		9(4.2)	50,0	66,5	0(0,0)	50.0	55,5	0(0,0)	50,0	55,5	0(0,0)
RT+HT		23(10.6)	69,9	69,3	1(4,3)	52,0	65,5	3(13,0)	48,0	65,5	3(13,0)
CMF+HT		20(9.3)	74,6	80,0	3(15,0)	58,3	75,0	5(25,0)	52,8	70,0	6(30,0)
RT+CMF+HT		10(4.6)	60,0	60,0	1(10,0)	60,0	60,0	1(10,0)	60,0	60,0	1(10,0)
None		66(30.6)	66,2	90,7	16(24,2)	61,3	87,6	18(27,3)	52,5	86,0	20(30,3)

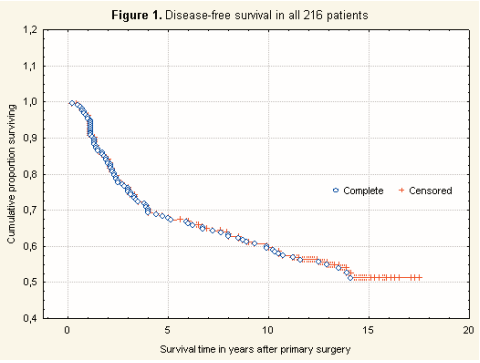
RT = Radiotherapy; CMF = Chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil;
HT = Hormone therapy; DFS = Disease-free survival; OS = Overall survival; LRR = Locoregional recurrences;
N = Number of patients. * p<0.05.

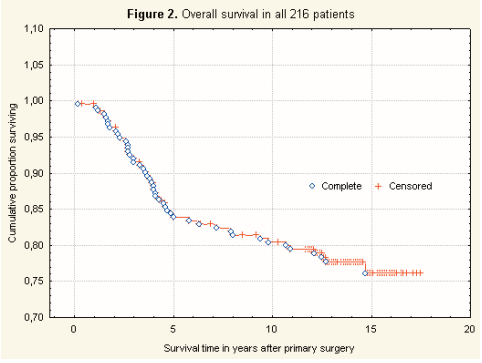
Outcome for nipple-areola complex

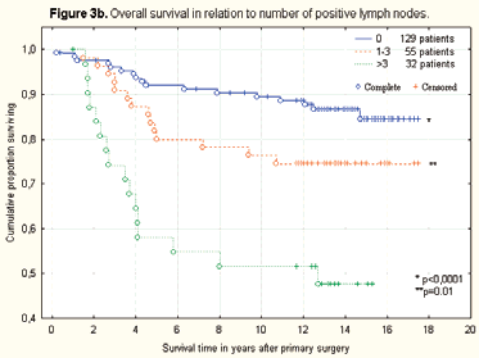
The NAC was removed in 11 patients (5.1%) at the primary operation because of a positive frozen section. Ten of these proved positive postoperatively (sensitivity 90.9%). In the 205 patients with a negative frozen section, three proved positive at the postoperative histopathological examination (specificity 98.5%). In these cases the NAC was removed soon after the primary operation. Necrosis was observed in the NAC postoperatively in 16 patients (7.9%). In two of these the necrosis was total, and the NAC was removed. In the other 14 it was

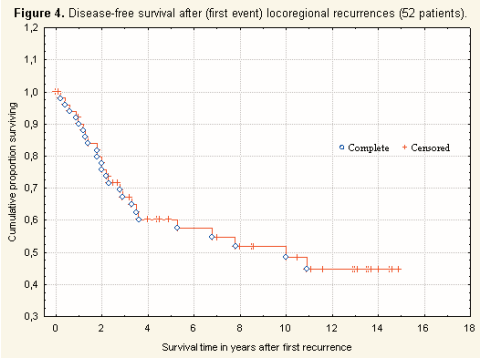
partial, and the NAC healed completely. During the monitoring period recurrences were observed in or at the NAC in eight of the 200 patients (4.0%) who still had this complex. In three of them only the NAC was removed, but the other five patients underwent salvage mastectomy. Salvage mastectomy was performed in six other patients because of recurrences in other parts of the breasts, but in one of these the NAC had previously been removed. Two patients underwent total mastectomy because of infection and one because of an unsatisfactory cosmetic result. Thus at the end of the monitoring period 184 patients (85.2%) had intact NAC.

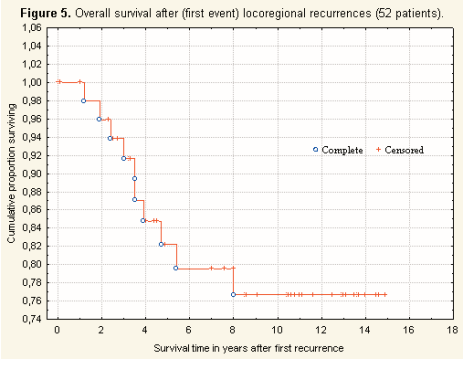
Graph 2. Overall survival and disease-free survival as explained in text above figures.

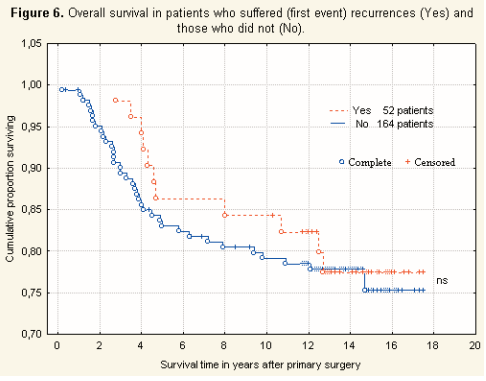












DISCUSSION

PAPER I

In most patients we found normal or only moderately raised touch thresholds outside the areola, especially on the medial side. On the areola and nipple higher thresholds were generally found but only 14% lacked touch sensibility (> 200 mN) on the nipple and 31% had normal values (< 3.2 mN). The lazy-S incision resulted in slightly better preserved sensibility on the medial and inferior part of the areola when compared to the inframammary incision. The location of the prosthesis (submuscular or subcutaneous) did not influence the results. The best sensibility was found in the group that underwent SRM (group B). In this group the median touch thresholds were within our normal limits at most test sites.
Our results correlate well with the anatomy of the nerves of the breast (Figures 7a and 7b). The final touch perception after a breast operation is of course a combination of the sensibility maintained and that regained by reinnervation postoperatively. Clearly it must be difficult to perform a subcutaneous mastectomy without severing the anterior ramus of the lateral cutaneous branch of the fourth intercostal nerve at its entrance into the breast or elsewhere during its course to the nipple-areola complex. As the rest of the breast skin is more richly and more superficially innervated, it retains its sensibility better than the NAC, which is mainly innervated by the fourth intercostal nerve.

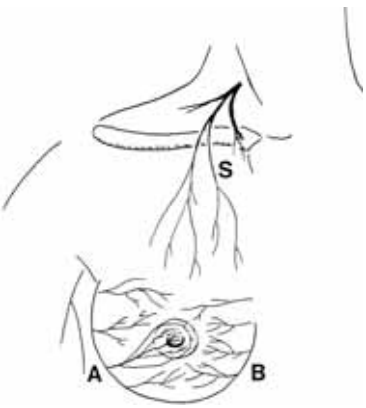


Figure 7a

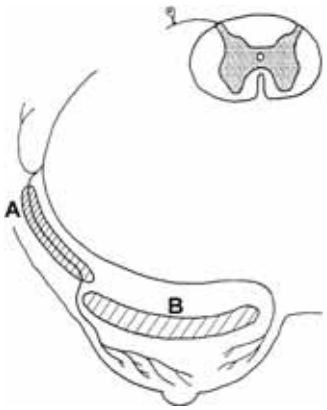


Figure 7b

The figures above show the innervation of the (right) breast.
A=Anterior rami of lateral mammary branches of the 4th intercostal nerve.
B= Medial mammary branches of intercostal nerves. C=Branches from the supraclavicular nerve.

The differences we found between patients with an inframammary incision and those with a lazy-S incision may be explained similarly. The inframammary incision often has to be extended quite far laterally to reach the axillary tail of the mammary gland. The route of dissection then obviously leads through the subcutaneous tissue at the entry of the important branch from the fourth intercostal nerve into the breast. We did not make any special effort to spare this nerve, simply because at that time we were not aware of its importance.
The more peripherally in the breast the nerves are severed during a breast operation, the more difficult will be the reinnervation of the nipple-areola complex. One would therefore expect the

reinnervation of the NAC to be less complete after NSN than after reduction mammaplasty, when it can begin at the edge of the areola. This is in accordance with our findings and those of others. Courtiss and Goldwyn [33] found unchanged sensation in the nipple and areola in 65% of their patients after reduction mammaplasty (transposition methods) but 'reasonable' sensation in the nipple and areola in only 25% of patients after subcutaneous mastectomy. They observed that the sensibility returned in the peripheral skin before it did in the nipple and areola. Other investigators have found that the sensibility often returns completely in breasts after pedicled reduction mammaplasty [34-36].
Several investigators have used von Frey's instrument to measure breast sensibility after reconstruction with musculocutaneous flaps. Slezak et a1. [13] examined ten patients after breast reconstruction with a pedicled TRAM flap and found no sensibility in two flaps and ten times higher touch thresholds than normal in the rest of the flaps. Other investigators have obtained similar results for measurements on TRAM flaps [37,38] and latissimus dorsi flaps [39]. None of these authors report any sensibility in the NAC of their patients' breasts.

PAPER II

We found no reduction in basal skin circulation in the breast after NSM, whether the breast had received RT or not, as compared with the contralateral breast at least 1 year after the operation or after RT. On the contrary, in the NAC there was a slight increase in skin circulation after RT. Even when the results were expressed as the ratio between the treated and untreated breast in order to reduce the biological and methodological variations, no reduction in skin circulation could be demonstrated. This study was done solely on breasts where the implants were placed subcutaneously. In an earlier study on breasts with the implants in a submuscular position Perbeck and al. [28] have shown a reduction of blood flow in the NAC to 13% as compared with the contralateral breast after SRM but no reduction when NSM had been done through a lazy-S-shaped incision. In another study [40] we examined the skin circulation at least 1 year after radiotherapy in patients treated with PM and found no reduction in skin circulation. It must be emphasised that we have not measured the subcutaneous blood flow or the skin circulation during any kind of challenge. It is possible that the ability to react to different kinds of provocation, e.g. traumatic hyperaemia or adaptive inflammation as part of the healing process, might be altered by RT.
With LDF, but not with FF, a two to three times higher skin circulation was found in the NAC compared with the area 2 cm above and below the border of the areola. These results are in agreement with earlier findings of increased skin circulation in the NAC compared with the surrounding areas, as measured by LDF [41] . There are several explanations for this discrepancy between the methods. First, laser LDF differs from FF by measuring a deeper circulation. How deep is a matter of controversy; 1–2 mm in the skin [42] but even down to 6 mm in the gastrointestinal tract [43] has been suggested. The blood flow velocity is much higher in the arterioles than in the capillaries, which means that the blood flow in the arterioles has much more influence on the laser Doppler signals than that in the capillaries, despite a larger capillary network. Second, it is likely that there is a true difference in circulation values between different layers of the skin, as has in fact been shown after NSM and especially after SRM, when the circulation is based on a wide vertical pedicle. In cases of epidermal necrosis of the NAC after this operation, FF showed no skin circulation in the complex, whereas with LDF signals were recorded [44].

PAPER III

We found a cumulative rate for capsular contracture of 20.6% and a significant difference between irradiated and non-irradiated breasts (41.7% v. 14.5%). However, patients with capsular contracture could be helped by a single corrective procedure, after which their breasts remained soft throughout the monitoring period (median 60 months). Similarly, Melmed [45] has reported an 87% success rate after open capsulotomy for capsular contracture in 62 breasts with a minimum monitoring period of 14 months. He replaced all of the implants, and even though he used polyurethane-covered implants, he placed them subglandularly and used an operation technique quite similar to ours. His is the only prospective study on the subject that we could find in the literature and the only one where saline-filled implants with textured surfaces were used, but Palmer et al. [23] in a study of subcutaneous mastectomy made on breast cancer patients, report that "Capsular contracture is readily corrected by open capsulotomy with excellent results and no complications".

In our opinion the cumulative rate of 20.6% CC in our study is quite satisfactory, considering that all the patients had breast cancer. Gabriel et al. [46] in a retrospective study of 749 women with breast implants monitored for five years, found that the CC-rate was significantly higher among those who had received implants after mastectomy (therapeutic or prophylactic) than for those operated on for cosmetic reasons only. Wickman [47] found a 33.5% CC rate in 50 breasts one year after tissue expansion. As for the use of saline-filled implants with textured surfaces in breast augmentation for cosmetic reasons, most investigators have found a CC-rate in the range of 8–15% [48-50] although some have reported a much higher frequency [51]. At first glance, a 41.7% rate of CC, as we found for irradiated patients, seems unacceptable. However, considering our, and other authors', good results with open capsulotomy, which is a fairly simple procedure that can be done as day surgery, we do not think that irradiation should be an absolute contraindication for this kind of breast reconstruction with implants. A standard primary breast reconstruction often implies a two-stage procedure with a tissue expander prosthesis followed by a permanent implant. NSM can be seen as a one-stage procedure that becomes two-stage in cases where CC develops.

Many other authors have examined the CC-rate in augmented breasts after RT. Most of these studies are retrospective and were performed on breasts with subpectorally-placed silicone prostheses, and most of them have demonstrated an increased frequency of CC after RT [52]. We found only two prospective clinical studies on the subject in the literature, both showing increased frequency of CC after RT [53,54].

Implants with small pore diameter (33 μm) on their textured surfaces seemed to be more favourable when it comes to avoiding CC than those with larger diameters (400 μm) and thus, fewer pores per cm^2. We found no other prospective clinical study in the literature directly comparing the CC-rate for prostheses with textured surfaces and different pore sizes. A prospective clinical study with more patients involved than in ours is clearly needed to settle this matter.

PAPER IV

NSM with a subcutaneously placed prosthesis necessitates the use of a prosthesis that causes minimal tissue reaction, as even a minor tissue reaction to the prosthesis results in an unfavourable change of the breast both in cosmesis and consistency. The Misti Gold II® implant with a textured surface had a significantly higher CC-rate than the saline-filled prosthesis with a textured surface measured by Baker's classification after one year, and the relative breast compressibility was also worse.

The poor results obtained with the Misti Gold II® prosthesis can be explained in several ways, including a strong tissue reaction to the content of the implant or its shell; overfilling of the implant by the manufacturers to 18% compared with a silicon gel prosthesis, making it not completely suitable for a subcutaneous location; or an increase in the volume of the prosthesis after implantation as a result of osmosis. After the report by Forsythe in 1994 [55] (which we obtained in early 1995) that the Misti Gold II® prosthesis increased in weight, we started to measure the volume of the prostheses removed and found an increase in volume in relation to the time that the implant had been installed. This successive increase in volume resulted in the removal of all Misti Gold II® implants within 40 months. According to the manufacturer, the osmotic content of the Misti Gold II® prosthesis has since been changed.
We wish to draw attention to the importance of the quality of new implants and to the responsibility of the manufacturers to try them out properly before they are recommended for routine use. At present, we do not consider that Misti Gold II® implants fulfil the criteria of implants that can be placed subcutaneously, and it is questionable whether they should ever be used, except in selected cases of breast augmentation. Severe CC causes the patient great discomfort and most often necessitates reoperation, at great cost to both the patient and society.

PAPER V

We had a 24.1% rate of LRR as a first event with a median follow-up of 13 years (15 years for those who were still alive at the last assessment). After 10 years of follow-up this rate was 20.8%. The 10-year DFS was 60% and OS 80.5%. Among irradiated patients the LRR rate was 8.5%. Only 47 patients (21.8%) received RT. Many of them did not, for various reasons, receive this until 6-12 months after the primary operation. Since we recruited our patients, the policy for giving RT after total mastectomy has been changed in Stockholm. Today RT is given to all patients with a tumour size exceeding 30 mm or with substantial multifocality, and to all lymph node positive patients. Had this policy been adopted for the patients in this study, approximately 65% of them would have received RT.
No patient had a recurrence behind the prosthesis, and a majority of the LRR were situated in the same quadrant of the breast as the primary tumour.
All the 52 patients with LRR as a first event were treated with salvage surgery, but MRM was performed in only six of them. It has been shown by others [56-58] that the type of salvage surgery does not seem to affect DFS or OS after locally recurrent breast cancer in patients previously treated with conservative surgery, at least not in cases of relatively small or late recurrences.

Comparison with MRM

Our results compare well with the results of other trials after MRM [59-65].
In Table 9 our results after 10-years follow-up among patients with high-risk (stage II-III) breast cancer are compared with those of two large Scandinavian studies on patients with high-risk breast cancer operated with MRM. There were 115 patients with stage II-III breast cancer in our study, 87 of them (75.7%) had lymph node metastases, and 46 of them received RT. Our methods and doses for RT (see the Methods section) were about the same as those used in the other two trials. The use of other adjuvant treatment is summarised in the table. Twelve of our patients did not receive any adjuvant therapy while all the patients in the other two studies received RT and/or other adjuvant therapy. Overgaard et al. [59,60], on behalf of the Danish Breast Cancer Cooperative Group (DBCCG), have carried out a very comprehensive study on high-risk breast cancer patients operated with MRM at various hospitals in Denmark between

1982 and 1990. Of those patients, 1.708 were premenopausal and were treated postoperatively with CMF, but 1.375 were postmenopausal and received HT. All of their patients were randomly assigned to receive RT or not. Overgaard et al. gave eight or nine cycles of CMF compared to our six. For HT they gave tamoxifen 30 mg daily for one year, whereas we gave 20 mg daily for two years. Of course, our patients were selected for RT while theirs were randomised. However, the results for LRR are strikingly similar between these two studies and confirm what many other authors have also found, that RT very effectively reduces the risk for LRR. According to Overgaard et al. it also improves OS, and the latest report from the EBCTCG group [21] seems to confirm this. As we did not randomise for RT we cannot draw any such conclusions from our results. In fact the non-irradiated patients in our study had significantly better OS than those who received RT, which is understandable, as they had a better prognosis initially.

Table 9. Comparison with total mastectomy in high-risk (stage II-III) breast cancer patients.

Investigator/ Year of publishing	Follow-up time	Surgery	Meno-pausal status	RT	N	Systemic adjuvant therapy (N)			DFS (%)	OS (%)	LRR (%)
						CMF	HT	None			
DBCCG/ 1999	10 years	Total mastect.	Premen.	RT+	852	852	0	0	48	54	9
				RT-	856	856	0	0	34	45	32
			Postmen.	RT+	686	0	686	0	36	45	8
				RT-	689	0	689	0	24	36	35
SBCG/ 1989	7 years	Total mastect.	Premen.	RT+	121	0	0	121	54	62	12
				RT-	158	158	0	0	61	68	18
			Postmen.	RT+	190	0	100	90	57	62	13
				RT-	237	237	123	0	36	54	25
Benediktsson & Perbeck/ 2007	10 years	Nipple-Sparing mastect.	Premen.	RT+	17	15	8	1	57	53	5.9
				RT-	42	27	23	8	44	75	35.7
			Postmen.	RT+	29	4	24	4	48	62	10.3
				RT-	27	6	21	4	64	84	22.7

DBCCG=Danish Breast Cancer Cooperative Group; SBCG=Stockholm Breast Cancer Group;
RT=Radiotherapy; RT+= Irradiated; RT-=Non-irradiated; N=Number of patients;
CMF=Chemotherapy with cyclophosphamide, methotrexate, 5-fluorouracile; HT= Hormone therapy;
LRR= Locoregional recurrence as a first event; DFS=Distant-free survival; OS=Overall survival.

The third trial listed in Table 9 was carried out by Rutqvist et al. [61] on behalf of the Stockholm Breast Cancer Group (SBCG) on high-risk breast cancer patients, 88% of whom had lymph node metastases. It was published in 1989, and the patients were recruited during 1976 through 1984. As in the Danish trial, the patients were randomised between RT or not, but all of the non-irradiated patients received CMF, and many of the postmenopausal patients received HT.
The mean follow-up time was 6.5 years, and the results are slightly better than in our study, at least for LRR. Rutqvist and Johansson [62] published in 2006 results from the same study with more patients added and a longer follow-up time. The trial was open for patient entry through May 1990 and now includes 547 premenopausal and 679 postmenopausal patients who have been followed up for 11-27 years (median 18.4). Among premenopausal patients a 44% OS rate and a 14% LRR rate was found in the RT group but 50% OS and 24% LRR in the CT group. Among postmenopausal patients a 40% OS rate (approximately) was found in both treatment groups, but a 12% and a 26% LRR-rate was found in the RT group and in the CT group, respectively.
In the same paper [61] in which the above study was originally reported, Rutqvist et al. report another study of 638 pre- and postmenopausal breast cancer patients, 37.3% of whom had positive lymph nodes. All underwent MRM and were then randomised between RT and no adjuvant therapy. They were recruited during 1971 through 1976 and followed up for 10-16

years (mean 13.5). Among node-negative patients the cumulative incidence of LRR (including patients who had failed distantly first) was 23% in the surgical control group versus 5% in the group treated with RT postoperatively. The corresponding figures for node-positive patients were 55% and 21% respectively. Rates of recurrence free survival and OS were approximately 63% and 73% for node-negative patients but 31% and 39% for node-positive patients, respectively. RT did not seem to affect OS in this study.
Other authors have published similar results after MRM [17,19,63-65] and after PM with or without postoperative RT [17-20].
As reported by Arriagada et al. [66] the Stockholm trials, as well as some others, have shown that lymph node positivity significantly increases the risk for LRR after MRM, and that the risk increases with an increased number of positive nodes. We were unable to confirm this after NSM (Table 7).
The LRR rate in our study was significantly lower for postmenopausal (19.0%) than for premenopausal patients (30.5%). Other investigators have found the same [67,68].

Nipple-sparing mastectomy

As mentioned in the introduction, NSM has been taken up in several places during the last 6 years [25-27]. The first published results are promising, but in those studies the patient selection was narrower than in our study (e.g no central tumours included), all patients were given radiotherapy (per- or postoperative), and the follow-up time is still much shorter. Petit et al. [26] have evaluated 64 of their patients with at least one year of follow-up for cosmetic results. Fifty-one of them (79.7%) rated it as good and only one as poor. We have in previous studies found good sensibility [9] and circulation [10] as well as an acceptable long-term rate of capsular contracture [11] in the operated breast after NSM.
In our study the specificity for frozen section underneath the nipple was 98.5%. Of the patients who kept their NAC at the primary operation, 4.0% had a recurrence at this site during the follow-up period (median 13 years). This shows, in our opinion, that frozen section is a safe method to decide whether to save the NAC or not.

Outcome after (first event) locoregional recurrences

Freedom from further LRR or DM after a first LRR was 60% and OS 82% at 5 years.
In our study the occurrence of LRR did not affect OS after primary surgery (Graph 2/Figure 6), but in accordance with findings of other investigators [67,69-82], OS was significantly worse for patients who suffered early LRR than for those who suffered it late.
Nielsen et al. [69] studied the outcome in 259 patients who suffered chest wall recurrences as a first event after MRM and found a 5-year OS rate of 43%, a 5-year probability of freedom from (further) LRR of 46% and a 5-year probability of freedom from DM of 29%. The survival rates for patients who had suffered axilla recurrences were about the same. Other authors have published similar results after LRR following MRM [70].
For LRR after conservative surgery, on the other hand, most authors have reported better survival rates [56,72-78]. In another Swedish study Fredriksson et al. [72] found breast cancer-specific survival of 84.5% at 5 years and 70.9% at 10 years after LRR in 391 women treated with PM and RT. In the USA Galper et al. [73] found an OS rate of 81% and a rate of freedom from further relapse of 65% at 5 years in 341 patients with LRR who were originally treated with conservative surgery and RT. These results are very similar to those in our study. Kurtz et al. [74] have stated that "recurrences in the breast following primary treatment with limited surgery and irradiation have a considerably more favourable prognosis than that of local failures after primary radical surgery". Recht et al. [76] have stated the same. We have found three reports of

comparisons of the outcome after LRR between initial treatment with PM and MRM [77-79]. In two of them [77,78] a significantly worse prognosis was found for chest wall recurrences than for breast recurrences after PM. Elder et al. [78] found a DFS rate of 49.4% and an OS rate of 68% at 5 years after a local breast recurrence, as opposed to corresponding figures of 33.1% and 50% respectively after a chest wall recurrence ($p<0.05$). van Tienhoven et al. [79], reviewing two randomised trials (EORTC 10801 and DBCG-82TM), report that the type of original treatment did not have any prognostic impact. The majority of the recurrences in these trials were early ones, which may have affected the results.

In our study only 7.7% of the (first event) LRR were located outside the operated breast. As reported by Wapnir et al. [67] the prognosis is much worse for those than for LRR located in the breast. This may partly explain the relatively good survival rates in our LRR patients.

CONCLUSIONS

The results from these trials on patients with breast cancer not suitable for partial mastectomy and operated on with nipple-sparing mastectomy and immediate breast reconstruction with implants, show that:

Postoperative touch sensibility is normal or subnormal in the skin outside the areola in most patients, but considerably reduced in the nipple-areola complex. As far as postoperative sensibility is concerned, the method is superior to modified radical mastectomy followed by breast reconstruction with a musculocutaneous flap. The loss of sensibility in the nipple-areola complex can be minimised by taking care to preserve the lateral mammary branch of the fourth intercostal nerve.

There are no long term changes in the skin circulation whether the breast is irradiated or not, but the circulation in the subcutaneous tissue has yet to be evaluated.

The rate of capsular contracture is acceptable if radiotherapy is not given. It is much higher in the irradiated breast, but in our opinion this procedure could still be an option, if the patients are well informed about the risks, monitored regularly and, if capsular contracture develops, operated on with open capsulotomy, which gives good long-term results.

Bioplasy Misti Gold II® prosthesis filled with a hydrogel can not be placed subcutaneously because of increase in volume, probably due to osmosis.

The operation is oncologically safe since survival is comparable to that after modified radical mastectomy and the consequence of locoregional recurrence (LRR) corresponds to that of LRR after partial mastectomy. The LRR-rate can be reduced substantially by giving radiotherapy to the operated breast.

GENERAL DISCUSSION

Cosmetically, our results were generally good. None of the present trials aims at proving this specifically, but we did send out questionnaires to most of our patients, and the results have been presented elsewhere [80]. Of 102 patients, 84% found the cosmetic results good or excellent, 95% considered immediate reconstruction a great advantage compared to a late one, and 92% of them would have recommended the same treatment to a friend with the same disease. The cosmetic results in six patients operated on with different methods are shown in Figures 1-5. As mentioned in the Methods section, about 80% of the patients were operated on as shown in Figures 4 and 5 with a submammary incision and a subcutaneously placed saline-filled implant (method D).

On the basis of our results and the above conclusions, we do not hesitate to recommend NSM for patients with breast cancer not suitable for partial mastectomy, at least if there is no skin invasion. Of course a biopsy for frozen section must always be taken from the area beneath the nipple, which in our study has proved to be a very efficient procedure (specificity 98.5%).

An option is to remove the NAC not only in cases of positive frozen section but always when the tumour is situated close to the areola, as others have done [25-27]. The operation will then become an “ordinary” skin-sparing mastectomy.

As to the reconstruction, we have only used implants and most often placed them subcutaneously. We have found that this gives very satisfactory cosmetic results in elderly patients who most often have ptotic breasts. For younger patients reconstruction with autologous tissues usually gives better cosmetic results. These techniques have improved much since we started our study in 1988, and as mentioned in the introduction, very few patients were then considered for this option.

There has also been great improvement in the making of implants since we started our trial. Before 1990 only silicon gel implants were available to be placed submuscularly, often necessitating an operation on the contralateral breast to achieve symmetry. With the development of saline-filled implants with textured surfaces the implant could be located subcutaneously, as we began to do in 1990 and which allows for better symmetry in cases of ptosis. By the introduction of anatomic cohesive silicon implants the cosmetic results can be further improved by locating the implant cranially beneath the major pectoral muscle which is sutured to the subcutaneous tissue and caudally just under the subcutaneous fat tissue layer giving the breast a natural ptosis. By using sterile sizers and having the patient in a sitting position a good apprehension of the final size and shape of the implant can be achieved.

Which skin incision is most suitable depends on various factors. The ideal incision in a patient with a 2-3 cm ptosis is, from a strict cosmetic point of view, 1.5 cm parallel to and above the submammary fold. With this incision the scar is completely hidden behind the lower part of the breast. A lazy-S incision from the upper part of areola and laterally results in a more visible scar but also in an easier dissection of the glandular tissue. With this incision it is very easy to remove the nipple and areola complex in cases of tumour overgrowth. The dissection in the subcutaneous layer along Scarpa’s fascia is also facilitated due to an excellent view, which is particularly important in patients with a thin layer of subcutaneous fat. The less one leaves behind of subcutaneous fat, the greater is the risk for necrosis. Through this incision it is also easier to spare the fourth intercostal nerve and thereby save more sensibility in the NAC, and even perform a sentinel node biopsy or axillary clearance through the same incision.

When SRM is needed, it should be based on a cranial pedicle which generally can be made shorter than a caudal one, thus lowering the risk of NAC-necrosis. However, as shown in Paper I, the risk for loss of sensibility in the NAC is probably less if a caudal pedicle is used. A very interesting refinement in SRM has been suggested recently by Hunter and Malata using the LeJour vertical mammaplasty skin pattern [81].

If RT is given there is a greater risk of CC. It is relatively easy to take care of this complication by open capsulotomy, excising the ventral surface of the capsule if necessary. There is seldom any need for a third operation. This procedure also makes it possible to change the size and shape of the implant, e.g. if the patient has gained weight and the symmetry is not perfect between the breasts.

Of the patients who received RT in this trial only 8.5% suffered LRR. As mentioned in the Discussion section in Paper V RT is given to far more breast cancer patients in Stockholm today than it was when the patients were recruited for this trial. Our results show that RT is not a contraindication for NSM. It has also become usual to give neoadjuvant chemotherapy to patients with large breast cancer tumours, which sometimes results in shrinking of the tumour to a size compatible with breast conserving surgery. This should further encourage surgeons to consider NSM instead of MRM when PM is not feasible.

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REFERENCES

1. ***Breasted JH*** (1930) The Edwin Smith surgical papyrus. The University of Chicago Press, Chicago, Ill.
2. ***Wood WC*** (1994) Progress from clinical trials on breast cancer. Cancer **74**:2606-9
3. ***Pearcy LT*** (1985) Galen, a Biographical Sketch. Archeology Nov/Dec 1985
4. ***Halsted WS*** (1894) The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. Ann Surg **20**:447-55
5. ***Patey DH, Dyson WH*** (1948) The prognosis of carcinoma of the breast in relation to the type of operation performed. Br J Cancer **2**:7
6. ***Veronesi U, Cascinelli N, Mariani L, Greco M et al*** (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med **347**:1227-32
7. ***Fisher B, Anderson S, Bryant J, Margolese RG et al*** (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med **347**:1227-32
8. ***Veronesi U, Paganelli G, Galimberti V, Viale G et al*** (1997) Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet **349(9069)**:1864-7.
9. ***Holmström H*** (1979) The free abdominoplasty flap and its use in breast reconstruction. An experimental study and clinical case report. Scand J Plast Reconstr Surg **13(3)**:423-7
10. ***Blondeel PN*** (1999) One hundred free DIEP flap breast reconstructions: a personal experience.Br J Plast Surg **52(2):**104-11
11. ***Arnez ZM, Khan U, Pogorelec D, Planisec F*** (1999) Breast reconstruction using the free superficial inferior epigastric artery (SIEA) flap.Br J Plast Surg **52(4):**276-9
12. ***Schneider WT, Hill HL Jr, Brown RG*** (1977) Latissimus dorsi myocutaneous flap for breast reconstruction.Br J Plast Surg **30(4):**277-81
13. ***Slezak S, McGibbon B, Dellon AL***. The sensational transverse rectus abdominis musculocutaneous (TRAM) flap: return of sensibility after TRAM breast reconstruction. Ann Plast Surg 1992; **28**: 210-17.
14. ***Rainsbury*** (2006) Skin-sparing mastectomy. Br J Surg **93(3):**276-81. Review
15. ***Singletary SE*** (1996) Skin-sparing mastectomy with immediate breast reconstruction: the M. D. Anderson Cancer Center experience. Ann Surg Oncol **3(4):**411-6
16. ***Becker*** (1984) Breast reconstruction using an inflatable breast implant with detachable reservoir. Plast Reconstr Surg **73(4):**678-83
17. ***Fisher B, Bauer M, Margolese R et al*** (1985) Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med **312(11)**:665-73
18. ***Uppsala-Örebro Breast Cancer Study Group*** (1990) Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Natl Cancer Inst **82**:277-282
19. ***Fisher B, Jeong J, Anderson S et al*** (1995) Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without radiation in the treatment of breast cancer. N Engl J Med **333**:1456-61
20. ***Liljegren G, Holmberg L, Bergh J et al*** (1999) 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Clin Oncol **17**:2326-2633
21. ***Early Breast Cancer Trialists´ Collaborative Group (EBCTCG)*** (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local

recurrence and 15-year survival: an overview of the randomized trials. Lancet **366**:2087-106

22. ***Hinton CP, Doyle PJ, Blamey RW et al*** (1984) Subcutaneous mastectomy for primary operable breast cancer. Br J Surg **71**:469-72
23. ***Palmer BV, Mannur KR, Ross WB*** (1992) Subcutaneous mastectomy with immediate reconstruction as treatment for early breast cancer. Br J Surg **79**:1309-1311
24. ***Al-Ghazal SK, Blamey RW*** (2000) Subcutaneous mastectomy with implant reconstruction: cosmetic outcome and patient satisfaction. Eur J Surg Onc **26**:137-41
25. ***Petit JY, Veronesi U, Orecchia R et al*** (2005) Nipple-sparing mastectomy in association with intra operative radiotherapy (ELLIOT): a new type of mastectomy for breast cancer treatment. Breast Cancer Res Treat **27**:1-5
26. ***Petit JY, Veronesi U, Luini A et al*** (2005) When mastectomy becomes inevitable: The nipple-sparing approach. Breast **14**:527-31
27. ***Caruso F, Ferrara M, Gastiglione G et al*** (2006) Nipple sparing subcutaneous mastectomy: Sixty-six months follow-up. EJSO **32**:937-40
28. ***Perbeck L, Proano E, Westerberg L*** (1992) The circulation in the nipple-areola complex following subcutaneous mastectomy in breast cancer. Scand J Plast Reconstr Hand Surg **26(2):**217-21
29. ***Gylbert L*** (1989) Applanation tonometry for evaluation of breast compressibility. Scand J Plast Reconstr Surg Hand Surg **23**:223–9
30. ***Perbeck L, Lund F, Svensson L, Thulin L*** (1985) Fluorescein flowmetry: a method for measuring relative capillary blood flow in the intestine. Clin Physiol **5**: 281–92
31. ***Sapirstein LA*** (1956) Fractionation of the cardiac output of rats with isotopic potassium. Circ Res **4**: 689–92.
32. ***Bone B, Aspelin P, Isberg B et al*** (1995) Contrast-enhanced MR imaging of the breast in patients with breast implants after cancer surgery. Act rad **36(2):**111-6
33. ***Courtiss EH, Goldwyn RM*** (1976) Breast sensation before and after plastic surgery. Plast Reconstr, Surg **58**:1-13
34. ***Gonzales F, Brown FE, Gold ME, Walton RL et al*** (1993) Preoperative and postoperative nipple-areola sensibility in patients undergoing reduction mammaplasty. Plast Reconstr Surg **92**:809-14.
35. ***Craig RDP, Sykes PA*** (1970) Nipple sensitivity following reduction mammaplasty. Br J Plas Surg **23**:165-72
36. ***Slezak S. Dellon AL*** (1992) Quantitation of sensibility in gigantomastia and alteration following reduction mammaplasty. Plast Raconstr Surg **91**:1265-9
37. ***Lapatto 0, Asko-Seljavaara S, Tukiainen E, Suominen E*** (1995) Return of sensibility and final outcome of breast reconstructions using free transverse rectus abdominis musculocutaneous flaps. Scand J Plast Reconstr Surg **29**:33-8
38. ***Liew S, Hunt J, Pennington D*** (1996) Sensory recovery following free TRAM flap reconstruction. Br J Plast Surg **49**:210-13
39. ***Peltoniemi H, Asko-Seljavaara S. Harma M, Sundell B*** (1993) Latissimus dorsi breast reconstruction: term results and return of sensibility. Scand J Plast Reconstr Surg **27**:127-31
40. ***Benediktsson KP, Celebioglu F, Perbeck LG*** (1997) Influence of radiation therapy on skin circulation in the breast after breast conservative surgery. Acta Oncol **36**:715–18
41. ***Proano E, Perbeck LG*** (1996) Influence of the site of skin incision on the circulation in the nipple-areola complex after subcutaneous mastectomy in breast cancer. Scand J Plast Reconstr Hand Surg **30**:195–200
42. ***Nilsson GE, Tenland T, Öbert PA*** (1980) A new instrument for continuous measurement of tissue blood flow by light beating spectroscopy. IEEE Trans Biomed Eng **27**:12–19.

43. ***Johansson K, Ahn H, Lindhagen J, Lundgren O*** (1987) Tissue penetration and measuring depth of laser Doppler flowmetry in the gastrointestinal application. Scand J Gastroenterol **22**:1081-8
44. ***Perbeck L, Proano E, Westerberg L*** (1992) The circulation in the nipple-areola complex following subcutaneous mastectomy in breast cancer. Scand J Plast Reconstr Hand Surg **26**:217–21
45. ***Melmed EP*** (1991) Treatment of breast contractures with open capsulotomy and replacement of gel prostheses with polyurethane-covered implants. Plast Reconstr Surg **86**:270–4 [see also 87:808, comment]
46. ***Gabriel SE, Woods JE, O'Fallon WM*** (1997) Complications leading to surgery after breast implantation. N Engl J Med **336**:677-82 (see also 718-9, comment)
47. ***Wickman M*** (1993) Comparison between rapid and slow tissue expansion in breast reconstruction. Plast Reconstr Surg **91**(4):663-70 (see also 671-2, discussion)
48. ***Coleman DJ, Foo IT, Sharpe DT*** (1991) Textured or smooth implants for breast augmentation? A prospective controlled trial Br J Plast Surg **44**:444–8.
49. ***Malata CM, Feldberg L, Coleman DJ, et al*** (1997) Textured or smooth implants for breast augmentation? Three-year follow-up of a prospective randomised controlled trial Br J Plast Surg **50**:99–105.
50. ***Pennisi VR*** (1990) Long-term use of polyurethane breast prostheses: A 14-year experience. Plast Reconstr Surg **86**: 368–71.
51. ***Tarpila E, Ghassemifar R, Fagrell D et al*** (1997) Capsular contracture with textured versus smooth saline-filled implants for breast augmentation: A prospective clinicalstudy. Plast Reconstr Surg **99**:1934–9.
52. ***Contant CM, van Geel AN, van der Holt B et al*** (2000) Morbidity of immediate breast reconstruction (IBR) after mastectomy by a subpectorally placed silocon prosthesis: The adverse effect of radiotherapy. Eur J Surg Oncol **26(4):**344–50
53. ***Von Smitten K, Sundell*** (1992) The impact of adjuvant radiotherapy and cytotoxic chemotherapy on the outcome of immediate breast reconstruction by tissue expansion after mastectomy for breast cancer. Eur J Surg Oncol **18**: 119–23
54. ***Krueger EA, Wilkins EG, Strawderman M et al*** (2001) Complications and patient satisfaction following expander/implant breast reconstruction with and without radiotherapy. Int J Radiat Oncol Biol Phys **49**:713–21
55. ***Forsythe R*** (1994) Bioplasty Misti Gold II breast implants. Plast Reconstr Surg **93**: 1530
56. ***Salvadori B, Marubini E, Miceli R et al*** (1999) Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. Br J Surg **86**:84-7
57. ***Kurtz JM, Amalric R, Brandone H et al*** (1988) Results of wide excision for mammary recurrence after breast-conserving therapy. Cancer **61(10):**1969-72
58. ***Kurtz JM, Amalric R, Brandone H et al*** (1991) Is breast conservation after local recurrence feasible? Eur J Cancer **27(3):**240-4
59. ***Overgaard M, Hansen PS, Overgaard J et al*** (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med **337(14):**949-55
60. ***Overgaard M, Jensen MB, Overgaard J et al*** (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomized trial. Lancet **353**:1641-8
61. ***Rutqvist LE, Cedermark B, Glas U et al*** (1989) Radiotherapy, chemotherapy and tamoxifen as adjuncts to surgery in early breast cancer: A summary of three randomized trials. Int J Radiat Oncol Biol Phys **16**:629-39

62. ***Rutqvist LE, Johansson H*** (2006) Long-term follow-up of the Stockholm randomized trials of postoperative radiation versus adjuvant chemotherapy among ”high risk” pre- and postmenopausal breast cancer patients. Act Oncol **45**:517-27
63. ***Feigenberg SJ, Mendenhall NP, Benda RK, Morris CG*** (2003) Postmastectomy radiotherapy: Patterns of recurrence and long-term disease control using electrons. Inj J Radiat Oncol Biol Phys **56(3):**716-25
64. ***Recht A, Gray R, Davidson NE et al*** (1999) Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without radiation: Experience of the Eastern Cooperative Oncology Group. J Clin Oncol **17(6):**1689-1700
65. ***O'Rourke S, Galea MF, Morgan D et al*** (1994) Local recurrence after simple mastectomy. Br J Surg **81(3):**386-9
66. ***Arriagada R, Rutqvist LE, Le MG*** (1999) Postmastectomy Radiotherapy: Randomized trials. Sem Rad Oncol **9(3):**275-86
67. ***Wapnir IL, Anderson SJ, Mamounas EP et al*** (2006) Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five national surgical adjuvant breast and bowel project node-positive adjuvant breast cancer trials. J Clin Oncol **24(13):**2028-37
68. ***Kurtz JM, Jacquemier J, Amalric R et al*** (1990) Why are local recurrences after breast-conserving therapy more frequent in younger patients? J Clin Oncol **8(4):**591-8
69. ***Nielsen HM, Overgaard M, Grau C et al.***(2006) Loco-regional recurrence after mastectomy in high-risk breast cancer-risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials. Radiother & Oncol **79(2):**147-55
70. ***Willner J, Kiricuta IC, Kölbl O (1997)*** Locoregional recurrence of breast cancer following mastectomy: Always a fatal event? Results of univariate and multivariate analysis. Int J Rad Oncol Biol Phys **37(4):**853-63
71. ***Freedman GM, Fowble BL*** (2000) Local recurrence after mastectomy or breast-conserving surgery and radiation. Oncology **14(11):**1561-81
72. ***Fredriksson I, Liljegren G, Arnesson LG et al*** (2002) Local recurrence in the breast after conservative surgery-a study of prognosis and prognostic factors in 391 women. Eur J Cancer **38(14):**1860-70
73. ***Galper S, Blood E, Gelman R et al*** (2005) Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. Int J Rad Oncol Biol Phys **61(2):**348-57
74. ***Kurtz JM, Amalric R, Brandone H et al*** (1988) Results of salvage surgery for mammary recurrence following breast-conserving therapy. Ann Surg **207(3):**347-51
75. ***Doyle T, Schultz DJ, Peters C et al*** (2001) Long-term results of local recurrence after breast conservation treatment for invasive breast cancer. Int J Rad Oncol Biol Phys **51(1):**74-80
76. ***Recht A, Schnitt SJ, Connolly JL et al*** (1989) Prognosis following local or regional recurrence after conservative surgery and radiotherapy for early stage breast carcinoma. Int J Rad Oncol Biol Phys **16:**3-9
77. ***Moran MS, Hafty BG*** (2002) Local-regional breast cancer recurrence: Prognostic groups based on patterns of failure. The Breast J **8(2):**81-7
78. ***Elder EE, Kennedy CW, Gluch L et al*** (2006) Patterns of breast cancer relapse. EJSO **32**:922-7
79. ***van Tienhoven G, Voogd AC, Peterse JL et al*** (1999) Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). Eur J Cancer **35(1):**32-8

80. ***Perbeck L, Westerberg L*** (1993) Subcutaneous mastectomy and immediate reconstruction in breast cancer. Abstract presented at the Nordic Surgical Society's Centennial Meeting in Copenhagen June 20th-23rd 1993
81. ***Hunter JE, Malata CM*** (2007) Refinements of the LeJour vertical mammaplasty skin pattern for skin-sparing mastectomy and immediate breast reconstruction. J Plast Reconstr Aesthet Surg **60(5):**471-81