DIFFERENT ASPECTS OF BREAST RECONSTRUCTION

Contralateral prophylactic mastectomy, postmastectomy radiotherapy, complications after biomaterials injection

Dmytro Unukovych

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To my mother
ABSTRACT

The advances in breast reconstruction and oncoplastic surgery have positively affected the cosmetic and functional outcomes without compromising oncological safety. In this thesis, different aspects and challenges of reconstruction of the breast have been addressed. Specifically, reconstructive outcomes and quality of life after contralateral prophylactic mastectomy in women with a personal and family history of breast cancer, the role of implant reconstruction in postmastectomy radiotherapy, and the management of complications after polyacrylamide gel injections are discussed.

In article I the clinical course of bilateral breast reconstruction and possible influence of adjuvant treatment were addressed in a consecutive series of patients with a personal and family history of breast cancer undergoing contralateral prophylactic mastectomy (CPM) during 1998-2008 (n=91). The findings indicated that CPM was a complex procedure, where the majority of patients (82%) received concurrent bilateral breast reconstruction. In addition, during the 3.9 years follow-up period more than half of the patients required at least one reconstruction-related operation. The clinical course after bilateral breast reconstruction was predominantly affected by operations on the cancer side, and reoperation was associated with radiotherapy. A protocol for management of patients opting for CPM and bilateral breast reconstruction is highly demanded.

In article II the psychosocial outcomes of CPM with reconstruction in patients with a personal and family history of breast cancer were assessed. In this prospective questionnaire study no negative changes in health-related quality of life, sexuality or body image were found. At the 2-year postoperative assessment, the patients showed a satisfactory quality of life similar to women in general population. However, CPM could have a negative impact on the particular aspects of body image including dissatisfaction with the body, appearance, scars, femininity, and attractiveness. Women considering CPM should be informed about the possible psychosocial implications and outcomes of the operation.

In article III the impact of immediate breast reconstruction with implants on dose distribution of radiotherapy was addressed in a cohort study of patients with (n=162) and without (n=558) breast implants. Overall, there was no difference in radiation doses to the organs at risk (ipsilateral lung and heart) between the two groups of patients. The presence of breast implants during radiotherapy planning was not associated with increased doses to ipsilateral lung and heart or decreased coverage of the target volume. Further studies specifically addressing consequences of radiotherapy with the longer follow-up will shed light on oncologic safety aspects.

In article IV the results from a retrospective multicenter study from Ukraine on patients with complications after breast augmentation with polyacrylamide gel (n=106) were evaluated. The injections were found to have caused irreversible damage to the breast in previously healthy women as they presented with multiple symptoms as pain (80%), breast deformity (73%), lumps (54%), and gel migration (37%). All patients necessitated gel removal with complex debridement operations; 39% with partial mastectomy, 7% with subcutaneous mastectomy; and 72% required a subsequent breast reconstruction. Public awareness of the potential hazards associated with injectables is warranted.
LIST OF PUBLICATIONS


III. Liljegren A*, Unukovych D*, Gagliardi G, Bjöhle J, Wickman M, Johansson H, Sandelin K. No difference in dose distribution in patients undergoing postmastectomy radiotherapy with or without immediate breast reconstruction with implants. *Manuscript*

* The authors contributed equally to this work

**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAA</td>
<td>Analytical anisotropic algorithm</td>
</tr>
<tr>
<td>BC</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>BCT</td>
<td>Breast-conserving therapy</td>
</tr>
<tr>
<td>BIS</td>
<td>Body image scale</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BPM</td>
<td>Bilateral prophylactic mastectomy</td>
</tr>
<tr>
<td>BR</td>
<td>Breast reconstruction</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Breast cancer susceptibility gene 1</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Breast cancer susceptibility gene 2</td>
</tr>
<tr>
<td>BRR</td>
<td>Breast reconstruction module of EORTC questionnaire</td>
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<tr>
<td>CBC</td>
<td>Contralateral breast cancer</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CPM</td>
<td>Contralateral prophylactic mastectomy</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical target volume</td>
</tr>
<tr>
<td>CW</td>
<td>Chest wall</td>
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<tr>
<td>DCIS</td>
<td>Ductal carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>DIEP</td>
<td>Deep inferior epigastric perforator</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose volume histogram</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>European Quality of Life Group Questionnaire</td>
</tr>
<tr>
<td>HAD</td>
<td>Hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>IBR</td>
<td>Immediate breast reconstruction</td>
</tr>
<tr>
<td>IMN</td>
<td>Internal mammary nodes</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>LD</td>
<td>Latissimus dorsi</td>
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<tr>
<td>MBROS</td>
<td>Michigan Breast Reconstruction Outcome Study</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NAC</td>
<td>Nipple-areola complex</td>
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<tr>
<td>NTCP</td>
<td>Normal tissues complications probability</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PAAG</td>
<td>Polyacrylamide gel</td>
</tr>
<tr>
<td>PMRT</td>
<td>Postmastectomy radiotherapy</td>
</tr>
<tr>
<td>PROMs</td>
<td>Patient-reported outcome measures</td>
</tr>
<tr>
<td>QUANTEC</td>
<td>Quantitative Analyses of Normal Tissue Effects in the Clinic</td>
</tr>
<tr>
<td>RIHD</td>
<td>Radiation-induced heart disease</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SAQ</td>
<td>Sexual activity questionnaire</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form-36 quality of life questionnaire</td>
</tr>
<tr>
<td>TM</td>
<td>Therapeutic mastectomy</td>
</tr>
<tr>
<td>TRAM</td>
<td>Transverse rectus abdominis muscle</td>
</tr>
<tr>
<td>$V_{20Gy}$</td>
<td>Volume irradiated with 20 Gray</td>
</tr>
<tr>
<td>$V_{25Gy}$</td>
<td>Volume irradiated with 25 Gray</td>
</tr>
</tbody>
</table>
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1 BACKGROUND

1.1 GENERAL BACKGROUND

Breast cancer (BC) is the most frequent cancer among women with an estimated 1.4 million new cancer cases diagnosed annually (25% of all cancers). Today, BC is considered the most common cancer form both in developed and developing countries. Incidence rates vary from 3.9 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. In 2008, the incidence in Sweden and in Ukraine was 79.7 and 40 per 100,000 women, respectively (Ferlay et al., 2010). Differences in health care systems and acceptance of screening programs, possibilities of diagnostics and treatment between countries affect outcomes in terms of prognosis, survival, as well as in the quality of life. Thus, well-functioning screening programs and public awareness of BC in Sweden have led to earlier diagnosis and increased BC survival rates than, for example, in Ukraine (Ferlay et al., 2010).

Curative treatment of BC requires surgery and often involves a combination of additional therapies as chemotherapy, radiotherapy, endocrine treatment, and immunotherapy. The additional treatment may be given preoperatively (neoadjuvant) or postoperatively (adjuvant).

In most cases, the women diagnosed with BC may choose between partial and total mastectomy. Partial mastectomy implies radical tumor removal thus preserving the remaining native breast. This technique is suitable for smaller tumors or the larger tumors that have been downsized by neoadjuvant treatment. Today, partial mastectomy followed by postoperative radiotherapy (i.e. breast-conserving therapy) is standard treatment and is proven to be non-inferior to total mastectomy in terms of survival and local recurrence (National guidelines for breast cancer care; Fisher et al., 2002; Veronesi et al., 2002). However, despite the acceptance of partial mastectomies, total mastectomy still accounts for about 50% in Sweden (National Breast Cancer Register. Annual Report, 2010). Mastectomy is indicated for patients with the larger or/and multifocal tumors, and some women with early stage breast cancer may actually prefer mastectomy to breast-conserving treatment (Gomez et al., 2010; Dragun et al., 2012).

The loss of a breast due to surgery constitutes a psychological and physical trauma and it has been shown to have an impact on quality of life and body image (Ganz et al., 1992; Rowland et al., 2000). Therefore breast reconstruction is essential to restore body image and improve quality of life after mastectomy.
1.2 BREAST CANCER SURGERY: FROM HALSTED TO ONCOPLASTIC TECHNIQUES

The contemporary history of BC surgery is strongly associated with a name of the American surgeon William Halsted, who based his surgical technique on the Virchow theory claiming that BC arose from epithelial cells and spread via lymphatic vessels. In 1882 Halsted presented and performed the first radical mastectomy at the Johns Hopkins Hospital (Halsted, 1894). Known as the radical mastectomy, it comprised en-bloc extirpation of the breast gland, the pectoral major and minor muscles and an extensive removal of axillary and adjacently located lymph nodes. This extensive procedure resulted in comparatively superior locoregional control of the disease and was globally adopted as a standard treatment for many years.

As a consequence of earlier diagnosis and available adjuvant treatment (radiotherapy, endocrine treatment in terms of surgical castration) the need for extensive operations subsequently diminished. In 1948 Patey and Dyson described a modification of the Halstedian operation and named it “modified radical mastectomy” suggesting preservation of the pectoralis major muscle, which significantly decreased postoperative morbidity and breast disfigurement (Patey and Dyson, 1948). In parallel, the possible utilization of radiotherapy as a treatment supplement was studied and later published by McWhirter in Scotland (McWhirter, 1955). These principles are considered to be fundamental for modern breast-conserving therapy, which became the treatment of choice for the majority of women with early-stage breast cancer. Another paradigm shift in breast surgery was the introduction of sentinel lymph node biopsy for staging early breast cancer (Giuliano et al., 1994; Veronesi et al., 1997). Its implementation reduced the risk of potential postoperative morbidity and unnecessary axillary dissection in node negative patients (Mansel et al., 2006). The application of oncoplastic surgery techniques further allows complete removal of the tumor with adequate surgical margins, and preserve the natural appearance of the breast (Clough et al., 2010).

1.3 BREAST RECONSTRUCTION

Breast implants: historical overview and modern devices

The Swedish chemist J. Berzelius isolated elemental silicon in 1824, and in the late 1800s the first silicon polymers were synthesized. During the World War II silicone gels were used by the surgeons, but late complications including diverse foreign-body reactions, ulceration, inflammation, and capsule formation were reported (Chasan, 2007).

In 1962 the first generation silicon rubber device was designed by Cronin and Gerow and in 1963 the first implant was placed into a patient (Braley, 1973).
Figure 1. Timeline and history of breast cancer surgery and breast reconstruction.

Since then, four other generations of implants have been developed. The advances primarily included improvements of materials, design and contour, so that the implantable devices could mimic the natural breast more closely.

At present, the following main types of implants (Figure 2) are used for the needs of breast restoration: 1) temporary expanders, 2) expandable implants, and 3) permanent implants. All three types of implants have an elastic silicone rubber shell in common, however their construction and utilization vary.

1) Temporary expanders are used for two-stage implant-based reconstruction. These devices allow the creation of a submuscular pocket of a suitable size and shape on the chest wall for future permanent implant placement. Tissue expansion is performed by expander inflation/deflation via an injection port that is either attached remotely (e.g. placed on the chest wall subcutaneously in the axillary area and connected with the device via a thin silicon tube) or is integrated into the expander. The remote port could be identified by palpation, whereas the integrated port has a magnet that greatly facilitates its location and injection.

2) Permanent expanders, or expandable implants, are designed for a definitive one-stage breast reconstruction, however their size may be adjusted during the expansion process. These devices contain two isolated shells, i.e. expandable with saline inner shell and prefilled with silicon gel outer shell. The permanent expander is inflated gradually over the period of several weeks. After the desired volume is reached, the injection port is removed under local anesthesia. Because of its dual-shell design, the expandable implant renders the potentially softer breast mound with the volume flexibility of a saline expander.
3) Permanent implants are pre-filled with a definitive volume of a cohesive silicon gel and are utilized for a single-stage breast reconstruction or at the second stage of implant-based reconstruction, when the appropriate pocket with an expander has been created.

Immediate breast reconstruction with implants

Any woman planned for a mastectomy may be a candidate for immediate breast reconstruction (IBR), however some contraindications exist. Oncological contraindications comprise patients with inflammatory cancer and those with identified regional or distant metastases. Active smokers, overweight patients, as well as those with co-morbidities are normally not regarded as appropriate candidates for IBR. Unrealistic or high expectations from the patient constitute another contraindication, which makes preoperative counseling about the outcomes of BR a prerequisite.

Therapeutic mastectomy incisions usually incorporate the skin overlying the tumor and nipple-areolar complex, but as little skin as possible should be excised, bearing in mind breast reconstruction. Skin-sparing mastectomy is essential when an implant-based reconstruction is planned, and several studies have shown this technique to be oncologically safe in patients with early stage breast cancer (Kroll et al., 1997; Sandelin et al., 2004; Eriksen et al., 2011). Another prerequisite for successful reconstruction is the total muscular coverage of the implant. For that purpose, the fascia of the pectoralis major muscle should be preserved. In the case of IBR with a permanent implant, the intraoperative use of a sizer (i.e. single-use temporary device)
may be helpful to evaluate the appropriate implant volume prior to its placement. When an expandable implant is being utilized, it should be filled with the adequate amount of saline that would allow skin closure with no extra tension.

Radiotherapy and other risk factors for complications

A recent meta-analysis of 1105 patients with breast reconstruction found that patients undergoing radiotherapy (RT) are 4.2 times more likely to experience surgical complications than patients without radiotherapy (Barry and Kell, 2011). The adverse effects of RT given both before and after breast reconstruction are well documented, and studies report 11–37% reconstruction failures in patients with implant-based reconstruction (Krueger et al., 2001; Cordeiro et al., 2004; Rusby et al., 2010). The irradiation of chest wall prior to reconstruction causes fibrosis of the tissues and loss of elasticity in the pectoralis muscle, which significantly complicates the surgical intervention and the course of postoperative tissue expansion (Lee et al., 2010). RT given on the implant may impair the aesthetic result leading to a 17-68% risk of capsular contracture and increase the probability of reoperation by 9-32% (Spear and Onyewu, 2000; Cordeiro et al., 2004; Behranwala et al., 2006; Benediktsson and Perbeck, 2006).

Potential side effects of radiotherapy are important to consider in patients undergoing bilateral breast reconstruction. The reconstruction outcomes on the two sides may be different as there is a substantial risk of not achieving a symmetric result (Figure 3). It has not been confirmed whether chemotherapy and/or endocrine therapy affect breast reconstruction outcomes (Alderman et al., 2002; Azzawi et al., 2010; Warren Peled et al., 2010).

Obesity or being overweight (BMI>25 kg/m²) at the time of operation is known to be associated with complications after breast surgery both with and without reconstruction (McCarthy et al., 2008b; Setala et al., 2009; de Blacam et al., 2012). Overweight patients have larger breasts and thus require larger excisions, which could partly explain the predisposition for wound infection, which can be particularly hazardous in the context of breast reconstruction (Berry et al., 2010).

Smoking is another well-known risk factor for postoperative complications. It is known to influence the microcirculation in the skin flaps, thus negatively affecting wound healing and predisposing to infection (Sorensen et al., 2002; de Blacam et al., 2012).

Therefore all candidates for breast reconstruction, as well as other women scheduled for breast surgery, should be encouraged to stop smoking and supported to lose weight.
In patients receiving RT after mastectomy, the outcome of autologous tissue reconstructions was found superior to implant-based procedures, regardless the consequence of radiation and implant placement (Kronowitz, 2012). Therefore, if RT is anticipated preoperatively, the possibility of delayed autologous breast reconstruction should be considered.

**Autologous tissue breast reconstruction**

The autologous tissue for BR may be grafted from the body as a free flap using microsurgical techniques or transferred on a pedicle based on blood vessels. The most common forms are the latissimus dorsi flap, the transverse rectus abdominis muscle flap, and the deep inferior epigastric perforator flap. The latissimus dorsi (LD) flap was described already in 1906 by Tansini and was rediscovered in the 1980s for the repair of chest wall radiation damage (Olivari, 1976). This flap is generally well suited for reconstruction when there is a skin deficiency, for example excision of large/multifocal tumors, multiple re-excisions, a tight mastectomy scar, or following radiotherapy (Menke et al., 2001). The LD flap has traditionally been reserved for delayed breast reconstructions or for cases of primary reconstruction failures. The LD itself rarely provides considerable volume and therefore permanent implant is often placed beneath the flap (Hammond, 2008).
The transverse rectus abdominis muscle (TRAM) flap grafting is technically much more difficult and is performed either as a pedicled flap or as a free microvascular flap (Holmstrom, 1979; Hartrampf et al., 1982). Due to the characteristics of fatty tissues transferred in the TRAM flap, the shape and consistency of the flap are similar to those of the normal breast.

The deep inferior epigastric perforator (DIEP) flap is based on the 1-3 perforators of the deep inferior epigastric vessels and offers the same benefits as the TRAM flap, but with less abdominal wall morbidity as the muscle is not sacrificed (Koshima and Soeda, 1989; Allen and Treece, 1994; Allen, 2003).

Nipple and areola reconstruction

The reconstruction of the nipple-areola complex (NAC) represents the final stage of BR and has been shown to have a positive impact on body image and satisfaction with the cosmetic results of the operation (Didier et al., 2012). NAC reconstruction is generally offered to all women undergoing a BR procedure and is performed under local anesthesia at a later stage after adjustments of the initial reconstruction are accomplished.

The techniques for nipple reconstruction comprise nipple sharing from the opposite side, local skin flaps (e.g. star flap), skin tattooing, or regrafting of a part of the original nipple after histopathological evaluation (Boccola et al., 2010). The areola may be successfully reconstructed by tattooing that enhances the skin color to match the areola of the opposite breast.

1.4 CONTRALATERAL PROPHYLACTIC MASTECTOMY

Prophylactic, or risk-reducing, mastectomy is the surgical procedure of breast removal offered to women with an increased risk of breast cancer.

Asymptomatic women with an increased risk of developing BC may opt for bilateral prophylactic mastectomy (BPM). Patients who have been diagnosed with BC in one breast (i.e. symptomatic) may choose contralateral prophylactic mastectomy (CPM) as an option to prevent BC in the opposite, contralateral, breast.

Indications for contralateral prophylactic mastectomy

To date, there are no absolute defined indications for CPM. Historically, the Society of Surgical Oncology published the Position Statement on Candidates for Consideration of Prophylactic Mastectomy in 1993 (Giuliano et al., 2007). Accordingly, CPM was indicated and could be considered in patients with unilateral breast cancer with: diffuse micocalcifications; lobular carcinoma in situ; large breast, difficult to evaluate; history of lobular carcinoma in situ followed by unilateral breast cancer; history of atypical hyperplasia, primary family history, and age at diagnosis < 40 years.
This Position Statement was updated in 2007 (Giuliano et al., 2007). Potential indications for CPM in patients with a current or previous diagnosis of breast cancer now included:

- Risk reduction in high-risk patients (i.e. BRCA mutations or other genetic susceptibility genes or strong family history with no demonstrable mutation)
- Difficult surveillance
- Reconstructive issues (i.e. symmetry, balance)

Risk for contralateral breast cancer

The estimated annual risk for developing contralateral breast cancer (CBC) in general population of BC patients accounts for 0.7% without a tendency to change with time (Adami et al., 1985; Gao et al., 2003). It is also known that women diagnosed with BC tend to overestimate their risk of contralateral events (Wood, 2009). Patients younger than 45 years have a 25% lifetime risk of developing contralateral metachronous cancer if they reach 75 years or more (Storm and Jensen, 1986). Interestingly, patients with DCIS have an annual risk of contralateral cancer (either in situ or invasive) at 0.6%, which is nearly the same as for primary invasive carcinoma, but overall mortality for DCIS patients is very low (Gao et al., 2003; Fisher et al., 2007).

Patients with a family history of BC do have an increased risk for CBC compared with the general population of BC survivors. This risk may vary depending on heredity as well as other risk factors. An earlier population-based study claimed that having one 1st-degree relative (e.g. mother or sister with BC) doubled the risk of CBC. Having both mother and sister with BC increased this risk by 5 times (Cook et al., 1996). Twin-studies on women with a family history of breast cancer show that annual risk of CBC is 1%. This risk is constant over time and does not depend on BC onset (Hartman et al., 2008).

There are several instruments for estimation of the BC risk in patients with a family history. The currently developed Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) is an example of a computer software available online at [http://ccge.medschl.cam.ac.uk/boadicea/](http://ccge.medschl.cam.ac.uk/boadicea/). This web application serves as a useful tool for primary oncogenetic counseling and it also calculates BRCA1/BRCA2 mutation probability (Antoniou et al., 2004).

To date, only BRCA1 and BRCA2 genes are screened for mutations in the target population on a large scale. Patients with hereditary non-BRCA1/2 breast cancer have the cumulative probability of developing CBC at about 27% in 20 years after the primary diagnosis (Shahedi et al., 2006). For BRCA1- and BRCA2 mutation carriers, 10-years risk of CBC is 43.4% and 34.6%, respectively (Metcalf et al., 2004). Table 1 summarizes the literature available on CBC risk among different risk groups.
Table 1. Contralateral breast cancer risk among different risk groups

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Reference</th>
<th>Annual risk</th>
<th>5 y risk</th>
<th>10 y risk</th>
<th>15 y risk</th>
<th>20 y risk</th>
<th>25 y risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>Brekelmans et al., 2007</td>
<td>0.7%</td>
<td>3.0%</td>
<td>5.0%</td>
<td>3.9%</td>
<td>4.9%</td>
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<tr>
<td></td>
<td>Shahedi et al., 2006</td>
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<td></td>
<td>Pierce et al., 2006</td>
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<tr>
<td>Non-BRCA1/2 hereditary BC</td>
<td>Brekelmans et al., 2007</td>
<td>1.0%</td>
<td>5.0%</td>
<td>6.0%</td>
<td>13.4%</td>
<td>24.2%</td>
<td>27.3%</td>
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<tr>
<td></td>
<td>Shahedi et al., 2006</td>
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<tr>
<td>BRCA1 hereditary BC</td>
<td>Brekelmans et al., 2007</td>
<td>3.1%</td>
<td>15.0%</td>
<td>20.0%</td>
<td>43.4%</td>
<td>48.0%</td>
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<td></td>
<td>Graeser et al., 2009</td>
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<td></td>
<td>Metcalfe et al., 2004</td>
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<tr>
<td>BRCA2 hereditary BC</td>
<td>Metcalfe et al., 2004</td>
<td>3.1%</td>
<td>17.0%</td>
<td>25.0%</td>
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Efficacy of contralateral prophylactic mastectomy

CPM is claimed to protect against contralateral breast cancer development by more than 90% (McDonnell et al., 2001; Goldflam et al., 2004; Herrinton et al., 2005). Compared to other preventive measures, prophylactic mastectomy gives the highest risk-reducing effect, mainly due to elimination of the glandular tissue. Systemic therapy including endocrine and/or chemotherapy was also shown to provide a substantial decrease of CBC risk, e.g. by 50% with tamoxifen alone (McDonnell et al., 2001; Quan et al., 2008). Bilateral prophylactic salpingo-oophorectomy, which is often considered by BRCA1 mutation carriers, may decrease the risk of CBC by 59% (Metcalfe et al., 2004). Intensive surveillance with annual mammography and MRI is another option that contributes to earlier cancer detection, however it does not prevent the disease itself (Samant et al., 2001).

Despite significant CBC risk-reduction, there is insufficient evidence whether CPM may improve survival, and if it does, for which population of breast cancer patients. The effect of CPM on survival is difficult to quantify due to the fact that the patients have a significant competing risk of death from distant metastases (Lostumbo et al., 2010). The largest retrospective matched-control study in 1072 patients undergoing CPM, demonstrated the association between CPM and decreased breast cancer mortality (Herrinton et al., 2005). In another study evaluating patients with a family history of BC (n=385), CPM was associated with improvement in both cancer-specific and overall survival (Boughey et al., 2010).
Technical aspects and outcomes of contralateral prophylactic mastectomy with reconstruction

A subcutaneous mastectomy is claimed to be appropriate for prophylaxis. Moreover, the nipple-sparing techniques may be applied due to the fact that BC incidence in the nipple was found to be rare (Yoshimura et al., 1996; Metcalfe et al., 2005). CPM may be performed at the time of primary BC surgery, concurrently, if the patient had gone through the genetic assessment. In practice, however, CPM is mostly recommended as a delayed intervention at a later stage after the primary cancer treatment is accomplished and the multidisciplinary counseling process with the risk estimation has been performed (Unukovych et al., 2012b).

Consequently, by the time of CPM women either present with a flat chest wall, some having received postmastectomy radiation, or with an irradiated conserved breast on the cancer side. Balancing these different conditions between the two sides constitute a surgical challenge (Figure 4).

Case-series assessing complications after CPM reported rates of reoperations from 4% in patients without reconstruction to 37% in those with reconstruction. The most frequent indication for reoperation was implant-related, which accounted for more than 50% of all reoperation reasons (Zion et al., 2003; Frost et al., 2005). A later study by Spear et al. concluded that breast reconstruction after prophylactic mastectomy was as safe as one after therapeutic mastectomy in terms of postoperative complications and patients' satisfaction (Spear et al., 2008).

Psychosocial implications of CPM have been scarcely addressed and the knowledge is based on few retrospective studies. Generally, women are highly satisfied with both the results of CPM and the decision to undergo prophylactic surgery, also reporting diminished concerns about developing BC after CPM (Frost et al., 2005; Geiger et al., 2006).

At the follow-up, however, the patients report several complaints regarding body image components and cosmetic outcomes (Montgomery et al., 1999; Hopwood et al., 2000; Geiger et al., 2006), although neither preoperative assessments nor multivariate analyses have been performed to measure the impact of CPM per se on these findings.
Figure 4. **Left:** a 42-year-old patient previously diagnosed with breast cancer and treated with mastectomy. Opting for contralateral prophylactic mastectomy due to a recently identified BRCA1 mutation. **Right:** the same patient, postoperative result after contralateral prophylactic mastectomy with concurrent bilateral breast reconstruction with implants. 
*Photography: courtesy of K. Sandelin*

1.5 PATIENT-REPORTED OUTCOME MEASURES

In recent years, a significant body of research dedicated to breast cancer has focused on measuring quality of life as well as other psychosocial outcomes. Assessment of patient-reported outcome measures (PROMs) may provide researchers with important information that complements what is known from the clinicians’ perspective.

**Health-related quality of life**

Quality of life is a definition that encompasses the components of general happiness and satisfaction with life. Health-related quality of life (HRQoL) regards the medical term for quality of life within clinical research and clinical practice (Fayers and Machin, 2007). HRQoL research is a relatively young scientific field, for which a demand has steadily grown in recent years. This could be attributed to the improvements in treatment, better survival and development of new drugs. Today, clinical trials should include information on how the studied treatment affects HRQoL in comparison to standard treatment or placebo/no intervention (Efficace et al., 2003).

HRQoL is a multidimensional structure comprising general health, physical, emotional, cognitive and social functioning, as well as specific aspects (i.e. symptoms and problems related to the disease). The development and design of a HRQoL instrument or its modules is a lengthy complex process involving 1) generation of HRQoL issues relevant to the selected patients, 2) construction of a professional questionnaire, 3) pretesting for accessibility
and relevance, and 4) field psychometric testing of reliability, validity and sensitivity (Sprangers et al., 1998).

Choosing the appropriate tool to measure HRQoL is a challenge (Bezjak et al., 2001). Single-item questions as well as ad hoc instruments are likely to be ambiguous and inadequate as they lack validity and reliability (McCarthy et al., 2008a). Instruments that assess HRQoL may be divided into generic that assess various diseases or healthy populations and disease specific. Two examples of widely used generic questionnaires are SF-36 and EQ-5D.

**SF-36**

Medical Outcomes Study 36-Item Short Form, or SF-36, is a self-administered tool that evaluates general health status and generic health concepts not specific to age, disease or treatment group (Ware and Sherbourne, 1992). SF-36 includes 36 items, defining eight HRQoL domains: physical functioning, role limitations due to physical problems, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, and general health perception (Figure 5). The questionnaire was translated into many languages with further validation in multi-cultural settings. Nowadays, normative data (i.e. country-specific data for healthy individuals of different sex and age) are available for most of the European countries (Sullivan et al., 1995).

**EQ-5D**

EQ-5D is a relatively simple and short generic instrument, applicable to a wide range of health conditions and treatments. It is characterized by the ease of administration, simplicity and international focus. The questionnaire comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and provides a simple descriptive profile and a single index value for health status (Brooks, 1996). The EQ-5D-3L records three levels of severity for each dimension of health, and a new 5L version details five levels for each dimension (Herdman et al., 2011).

Other psychosocial outcomes

**Anxiety and depression**

The prevalence of clinically relevant levels of anxiety and depression in cancer patients is up to 45%. Among breast cancer patients who accomplished their treatment about 30% will continue experiencing anxiety and depression at follow up (McDaniel et al., 1995), making these psychosocial domains important PROMs.
One of the most widely used instruments for the assessment of anxiety and depression is the Hospital Anxiety and Depression Scale (HAD). It was initially designed to detect clinically relevant anxiety and depression in non-psychiatric patients. The 14 questions in HAD exclude items of somatic symptoms of anxiety and depression, which makes it useful among somatically ill patients. Cut-off levels for clinical levels of anxiety and depression have been specified (Zigmond and Snaith, 1983).

**Figure 5.** The measurement model of SF-36 questionnaire. *Adapted from Ware et al. 1992*
Body image and sexuality

Body image is a subjective evaluation of a person’s physical appearance. Dissatisfaction with body image is a common side effect of cancer and its treatment (DeFrank et al., 2007). Hair loss, weight changes, scarring, changes in breast appearance, or loss of a body part (e.g., breast) may result in disturbing physical and psychological difficulties. In the publications dedicated to breast cancer, body image is often addressed together with sexual functioning. Numerous studies have found that women who received mastectomy reported more problems with body image and sexuality than do those with breast-conserving therapy (Ganz et al., 1992; Rowland et al., 2000; Brandberg et al., 2008; Brandberg et al., 2012). This knowledge becomes particularly important and may be applied in the preoperative counseling, when a patient is choosing between breast conservation, mastectomy or mastectomy plus reconstruction.

The Body Image Scale, BIS, assesses the impact of surgery on patients’ self-consciousness, physical and sexual attractiveness, femininity, satisfaction with body and scars, body integrity, and avoidance behavior. The 10-item scale is scored from 0 (not at all) to 3 (very much). The sum of the BIS-items gives an overall score (range 0-30) (Hopwood et al., 2000).

A tool for measuring sexual functioning is the Sexuality Activity Questionnaire, SAQ. It includes 10 items assessing sexual activity and is divided into three sections: pleasure (desire, enjoyment and satisfaction), discomfort (dryness, pain), and habit (sexual behavior) (Thirlaway et al., 1996). The pleasure section includes 6 items (scores: from 0 to 18), the discomfort section- two items (scores: from 0 to 6), and the habit section- one item (scores: from 0 to 3). The sum of all items within each section produces the three overall scores.

Patient-reported outcome measures in breast reconstruction

For patients choosing breast reconstruction versus mastectomy alone, quality of life and satisfaction with breast appearance are key considerations, and the women themselves may provide data regarding a unique perspective on the results of reconstruction (Pusic et al., 2007a).

There is a current belief that mastectomy as well as breast reconstruction has a strong impact on HRQoL, body image and sexuality (Lee et al., 2009). The existing HRQoL questionnaires are not sufficiently sensitive to detect possible changes following breast reconstruction, as they have not been designed specifically for that purpose (McCarthy et al., 2008a). Thus, in light of the scant evidence, the available literature on HRQoL and satisfaction with breast reconstruction should be interpreted with caution (Lee et al., 2009; Winters et al., 2010).

Two questionnaires for specific evaluation of breast reconstruction outcomes have been developed: the Michigan Breast Reconstruction Outcomes Study (MBROS) and the BREAST-Q (Chen et al., 2010). Though, there is currently no validated European
breast reconstruction-specific instrument, the EORTC Breast Reconstruction Module is currently in phase III of its development (Thomson et al., 2012).

The MBROS Questionnaires

In 1999 the Michigan Breast Reconstruction Outcomes Study (MBROS) was initiated and resulted in the development of two instruments evaluating satisfaction and body image. The MBROS Satisfaction and the MBROS Body Image Questionnaires are two independent tools that assess 7 items of patient satisfaction and 9 items of body image, respectively. All items in the questionnaires were generated by an expert panel, and neither patient interviews nor any item reduction had been performed (Wilkins et al., 2000). The MBROS was the first study addressing the issues of breast reconstruction. However the limitations in questionnaires’ development and psychometric testing restrict their use in clinical practice (Pusic et al., 2007a).

The BREAST-Q

The BREAST-Q is a patient-reported outcome instrument that was designed to measure both generic and breast surgery-specific domains. There are currently four modules: breast reduction, augmentation, reconstruction, and mastectomy without reconstruction. Each module includes a core of independent scales that assess six domains (satisfaction with breasts, satisfaction with overall outcome, psychosocial well-being, sexual well-being, physical well-being, and satisfaction with care). In 2009, the questionnaire was validated in the USA; however, it is less appropriate for use in routine clinical practice, i.e. individual assessment, as it was developed for group-level-based research only (Pusic et al., 2007b; Cano et al., 2012).

The EORTC Breast Reconstruction Module

In 2008, the development of the EORTC HRQoL module for breast reconstruction (BRR) was initiated. The BRR was designed to evaluate the benefits of breast reconstruction, to assess the relative benefits of different types of reconstruction as well as the timing of surgery (Thomson et al., 2012). Today, the provisional module comprises 31 items with the 5 hypothesized domains: treatment or surgery related items, body image, sexuality, cosmetic outcome and satisfaction. The BRR module is to be used alongside the EORTC generic QLQ-C30 questionnaire and disease-specific BR23 questionnaire (EORTC QLQ-C30 Questionnaire Modules). This is highly advantageous in the context of adjuvant therapy, which may potentially have adverse effects on HRQoL up to 12 months postoperatively and beyond (Winters and Thomson, 2011). Another advantage is that this module can be used to assess PROMs in women undergoing therapeutic mastectomy as well as prophylactic surgery. The third phase of BRR development is currently in progress and involves four countries in Europe with cross-cultural applicability to studies and trials (Thomson et
al., 2012). By comparison, neither the MBROS nor the BREAST-Q questionnaires have been validated for patients undergoing breast reconstruction in Europe.

**Photographic documentation**

This is a qualitative measurement of the outcome that usually relies on four to six standardized clinical photographs taken from different angles. Preoperative may serve as useful tools for operative planning, discussions at the multidisciplinary conferences and in surgical teams. The pictures document the qualitative breast characteristics such as symmetry, shape, size, scars etc. Photo documentation should ideally be performed before and after surgery, especially in non-typical cases (e.g. as presented on Figure 16).

However, photographic assessment is essential not only for the individual evaluation of aesthetic outcome, it also helps to compare the outcomes of different reconstruction techniques on a group level. For research purpose, postoperative photos are shown to an expert panel usually consisting of healthcare professionals who are familiar with breast reconstruction. Often, the expert opinions about the reconstructive outcomes are divergent from the patients’ perspective (Eriksen et al., 2012; Lindegren et al., 2012). Finally, the pictures may serve as a useful tool in preoperative consultation to demonstrate a difference between the techniques and to show possible outcomes of breast reconstruction.

### 1.6 POSTMASTECTOMY RADIOThERAPY

Radiotherapy after mastectomy, or postmastectomy radiotherapy (PMRT), reduces the risk of locoregional recurrence and improves overall survival, especially in women with node-positive breast cancer (Clarke et al., 2005). Recent evidence that radiotherapy (RT) is also beneficial for patients with one to three involved nodes or those with high-risk node-negative disease has extended the application of PMRT (Veronesi et al., 1997; Karlsson et al., 2007).

During the preoperative planning it is often not clear whether the patient will be recommended PMRT or not as this decision is dependent on the histopathology of the breast, tumor biology and the axillary status. Currently, women operated with total mastectomy in the absence of contraindications are offered breast reconstruction (National guidelines for breast cancer care; National Institute for Health and Clinical Excellence. Early and locally advanced breast cancer). Therefore, issues of integrating of radiotherapy and reconstructive surgery constitute a clinical challenge, considering reconstruction timing (immediate vs. delayed), type (implant vs. autologous) and staging (one-stage vs. two-stage).

Comprehensive PMRT planning is based on the three-dimensional computer tomography (3D CT) technology, which provides the dose distribution in the target volume and organs at risk based on the individual anatomical information. Furthermore, different RT techniques (e.g. conventional, intensity-modulated), beams
(e.g. photon, electron, or a combination), and energies (e.g. 6-MV, 15-MV, 18-MV, or a combination) exist. Their utilization varies widely between the radiotherapy departments worldwide. But the ultimate goal of PMRT is the complete dose coverage of the target volume (i.e. ipsilateral chest wall) and the avoidance of radiation to the organs at risk (i.e. heart, lung, the opposite breast).

Clinical target volume

After mastectomy, patients may require radiotherapy either to the chest wall (CW) in node-negative disease or chest wall plus lymph nodes (CW+lymph nodes) in node-positive disease. Correspondingly, the target volume of tissues for the irradiation is defined as the clinical target volume, CTV (ICRU 62: Prescribing, recording and reporting photon beam therapy (supplement to ICRU report 50), 1999).

CTV for local radiotherapy usually comprises chest wall alone, while CTV for locoregional RT additionally covers also regional lymph nodes, incl. axillary, infraclavicular and supraclavicular region (Figure 6). The irradiation of the internal mammary lymph nodes (IMN) is controversial and its benefit remains unclear (Matzinger et al., 2010).

CTV should be encompassed by 95-105% of the prescribed dose, i.e. 45-55 Gy (National guidelines for breast cancer care). In patients receiving IBR with implants, CTV may include the breast implant as presented on Figure 8, or it may be delineated separately.

In practice, the radiation treatment plan is assessed using Dose Volume Histograms (DVHs). DVH is a summary of the 3D dose distribution in the 2D format (Figure 7). DVH allows controlling that CTV is irradiated by \( \geq 95\% \) of the prescribed dose (CTV \( V_{95\%} \)) and that the dose-volume limits to the organs at risk are respected.

Organs at risk

Ipsilateral lung

One of the most common RT-induced lung reactions is radiation pneumonitis. Although the RT-induced injuries of the lung were shown to correlate with the total dose given to the lung and with the irradiated lung volume (Lind et al., 2001), the dose-volume response constraints are not univocally determined. One of the constraints suggested by the QUANTEC review, which summarized the most relevant literature on the subject, was \( V_{20Gy} \leq 30-35\% \) (Marks et al., 2010).

Heart

Radiotherapy can cause a variety of cardiac diseases such as coronary artery disease, cardiomyopathy, and conduction disorders, which are grouped as radiation-induced heart disease (RIHD).
Figure 6. 3D CT-based postmastectomy radiotherapy planning.
Locoregional (chest wall plus lymph nodes) left-sided plan:
clinical target volume (delineated in orange), heart (in violet), ipsilateral lung (in blue).

Figure 7. Dose volume histogram for a left-sided locoregional treatment plan.
The curves represent dose-volume distribution for clinical target volume (orange),
left lung (blue), and heart (red).
The risk of RIHD is shown to be dependent upon the volume of the heart exposed to radiation and the dose received by that volume (Hajris et al., 1999). Older methods of delivering RT resulted in more extensive cardiac irradiation and higher RIHD risk than it is seen with the current techniques (Schmitz et al., 2012). The dose-volume response relationship for heart irradiation is specifically summarized in the QUANTEC issue (Gagliardi et al., 2010).

Dose constraints can be generally defined in physical terms (as a defined dose to a defined volume), or in radiobiological terms. In the latter case normal tissues complications probability (NTCP) is calculated, based on the dose-volume response curve of the specific endpoint. Long-term cardiac mortality is an endpoint of great relevance in PMRT. For partial irradiation, for example, NTCP model-based estimates predict that a $V_{250cGy} < 10\%$ (in 2 Gy per fraction) will be associated with a $<1\%$ probability of cardiac mortality 15 years after RT (Gagliardi et al., 2010).

The recommended heart constraints during PMRT are defined differently in the national guidelines, i.e. in Denmark: $V_{250cGy} < 10\%$ (OBCG Guidelines for postoperative radiotherapy of breast cancer), in Norway $V_{250cGy} < 5\%$ (NCG Guidelines for postoperative radiotherapy).

Finally, at the RT planning dosimetric heart restrictions should be also considered in relation to the cardiac toxicity caused by the given or anticipated chemotherapy agents (e.g. anthracyclines, trastuzumab) and to other cardiovascular risk factors.

**Breast reconstruction with implants and postmastectomy radiotherapy**

For radiotherapy planning, the presence of an implant implies a displacement of soft tissues within CTV as opposed to the absence of an implant. Thus, in patients with a
reconstructed breast, the treatment planning might be complicated by the distortion of the chest wall anatomy brought on by the sloping shape of the implant. These geometrical changes affect the shape of the target volume, require more complex planning techniques, and may potentially increase lung and heart irradiation (Buchholz et al., 2002). However, no convincing evidence exists in the literature, as the impact of breast implants on planning of PMRT has not been studied in detail. The largest case-control study of patients with PMRT receiving implant-based IBR (n=196) concluded that breast reconstruction was associated with excellent chest wall coverage and acceptable doses to heart and ipsilateral lung (Ohri et al., 2012).

Another potential problem in PMRT planning is seen in patients reconstructed with temporary expanders with an integrated port. Although the integrated magnetic port simplifies the process of expansion by facilitating the location of the injection port (Elliott and Dubrul, 1988), the presence of a magnet during breast imaging leads to artefacts (Fagan et al., 1995; Nava et al., 2012). This may limit the utilization of these implants, especially in cases when radiotherapy is anticipated (Figure 9).

Furthermore, several experimental studies report perturbation in dose distribution in the volume around the magnet. This results in underdosage in the direct shadow of the metallic port: 22-30% for the single 6-MV photon beam and 7-13% for the two tangential 6-MV photon beams (Moni et al., 2004; Thompson and Morgan, 2005; Damast et al., 2006; Chatzigiannis et al., 2011). The clinical implications of this underdosage, however, have not been studied in detail and remain unclear.

![Figure 9. 3D CT-based radiotherapy planning in a patient with the temporary expander. Artefacts caused by the integrated magnetic port (marked with X) are seen as irregularities on the CT image.](image_url)
1.7 BREAST INJECTIONS WITH BIOMATERIALS

Polyacrylamide gel as a biomaterial for injections

An optimal biomaterial for breast enhancement and correction has been sought through centuries. Paraffin, petrolatum, vegetable oil, lanolin, beeswax, Bioplast, and liquid silicone are examples that initially seemed promising, but in the long term all led to unfavorable results with serious side effects (Chasar, 2007).

Polyacrylamide gel (PAAG) for injections was introduced in Ukraine and Russia in the 1990s as a potential biomaterial for "non-invasive breast augmentation".

In general, polyacrylamide is used for industrial purposes, e.g. soft contact lens production, in electrophoresis systems or as a culture medium in laboratory experiments. Polyacrylamide is synthesized by cross-linking polymerization of acrylamide (Figure 10).

![Figure 10. Monomer of polyacrylamide.]

PAAG is a jellylike transparent substance containing about 0.5%-5% of polyacrylamide and more than 95% of water. Polyacrylamide in this compound has not been shown to be toxic or carcinogenic in several animal studies (Amended final report on the safety assessment of polyacrylamide and acrylamide residues in cosmetics). However, no clinical trials on PAAG safety for humans have been carried out.

Free Internet search shows that different brands of polyacrylamide gel for soft tissue augmentation exist in the world. In China, it is known as Aomiding; in Russia and Eastern Europe it is branded as Formacryl, Bioformacryl, or Arigiform; in other countries- Outline, Amazing Gel, and Bio-Alcamid. Presumably, thousands of women have undergone PAAG injections in Asia and some European countries (Cheng et al., 2002; Christensen et al., 2003; Cheng et al., 2011).

In Ukraine, a novel and relatively cheap procedure of PAAG injection was mainly performed in private medical centers, it did not require general anesthesia nor any advanced skills from the physicians (Kovanskaya, 2000). The gel was injected with a needle freely and no "real fibrous capsule around the masses was formed (Christensen et al., 2003). Preoperative breast imaging may identify multiple areas throughout the whole breast gland and within the pectoralis major muscle (Teo and Wang, 2008). In less complicated cases, PAAG is predominantly located in the retromammary space and is seen as a single gel collection in front of the fascia pectoralis (Figure 11a).

Some patients, however, present with gel probably having been injected behind the pectoralis fascia and even into the glandular tissue, where mammographic findings show multiple bizarre opacities throughout the breast parenchyma (Figure 11b).
Figure 11a. Mammography image of a patient with polyacrylamide gel injections. The injected biomaterial is seen as a gel collection that migrated caudally.

Figure 11b. Mammography image of a patient with free biomaterial injections bilaterally. The gel is multifocally located throughout breast parenchyma.

*Images: courtesy of B. Hedison*
On MRI, PAAG deposits has been shown to be located intra- and retroglandularly, intra- and retropectorally, or subcutaneously. Besides, gel migration to the shoulder or neck, over the sternum or even into the extrapleural space has been described (Lui et al., 2008).

At the open surgical procedure, the gel is found within different layers. During the extraction, PAAG varies in consistency being sticky, firmer, or fragile. The color is either transparent, milky white, or yellow and often has a bloody tint. When not presented in a mass, the gel appeared as elongated deposits splitting up the connective tissue or the fat cells (Christensen et al., 2003).

Histopathology and cytological examination of the tissues surrounding PAAG revealed foreign body reaction (histiocytic and multinucleated foreign body-type giant cells) or chronic/acute inflammation reaction (lymphocytes, plasmocytes and eosinophils between and surrounding gel pools). In the absence of foreign body- or inflammation reaction, the larger gel pools were surrounded by a thin 30-50 microns fibrous capsule (Leung et al., 2007).

Complications after polyacrylamide gel injections

Adverse effects and long-term complications of PAAG used for breast augmentation have been scarcely studied and reported. These complications mainly included pain, gel migration, breast disfigurement, firmness, breast lumps, and in some cases inflammation and infection (Cheng et al., 2002; Cheng et al., 2006; Kang and Ong, 2011; Xu et al., 2012). Specific complications like late hematoma, seroma and galactocele after PAAG injection are also described (Cheng et al., 2011). However, there is also a group of asymptomatic women with acceptable results from PAAG injections who do not have any complaints and are satisfied with the outcomes. In these patients, gel masses bring diagnostic dilemmas for breast imaging, i.e. ultrasound, mammography or MRI (Lui et al., 2008; Teo and Wang, 2008).

The global public awareness of PAAG injections and their possible complications have been discussed only recently (van Dam et al., 2009; Luo et al., 2010; Unukovych et al., 2012a). Most of the authors strongly advise that PAAG is unsuitable for breast augmentation.

Management of complications and breast reconstruction

There is no standard approach how to deal with PAAG complications as the symptoms vary considerably. The reported experience is limited primarily due to the low number of treated patients.

The complications have been shown to require complex open surgery with gel removal. PAAG extraction using an aspiration method is not efficient as there are still gel residuals in the breast tissue, even after several suction procedures (Zhao et al., 2004; Qiao et al., 2005). Due to the widespread and extreme multifocality of the gel deposits both sagittally and frontally, even open surgery does not guarantee complete gel removal (Qiao et al., 2005; Luo et al., 2010; Unukovych et al., 2012a). An open
debridement operation permits extraction of as much gel as possible and the removal of glandular tissue if necessary.

In patients who require breast restoration after gel removal and partial/total mastectomy, breast reconstruction with implants may be considered because the skin envelope is preserved in most cases. A two-stage surgery with initial debridement followed by delayed breast reconstruction is preferable, especially in the cases where the gel has migrated within the breast gland and into the pectoralis muscle, or in cases of inflammation.
2 AIMS OF THE THESIS

The overall aim of this thesis was to evaluate outcomes and elucidate the challenging aspects of breast reconstruction in different clinical situations, such as contralateral prophylactic mastectomy, postmastectomy radiotherapy, and complications after polyacrylamide gel injections. The specific aims were:

• to evaluate the clinical course of breast reconstruction in patients with a personal and family history of breast cancer undergoing CPM, and to elucidate the association between reoperation and adjuvant therapy (Study I)

• to prospectively assess the quality of life, anxiety and depression, sexuality and body image in patients with a personal and family history of breast cancer undergoing CPM with immediate breast reconstruction. To determine the cosmetic outcome and satisfaction with the breast reconstruction on the prophylactic side and the cancer side (Study II)

• to evaluate if the presence of breast implants during postmastectomy radiotherapy has an impact on the dose distribution to the organs at risk (ipsilateral lung and heart) and the irradiated target volume (Study III)

• to describe a large cohort of patients with a wide spectrum of complications after PAAG injections, focusing on the management and debridement operations, and to evaluate the outcomes of breast reconstruction, as well as patients’ health related quality of life and satisfaction (Study IV)
3 PATIENTS AND METHODS

Illustration of the patients included in this thesis (Study I, II, III and IV).

CPM contralateral prophylactic mastectomy, IBR immediate breast reconstruction,
PAAG polyacrylamide gel, RT radiotherapy.

3.1 STUDY I

This is a descriptive retrospective study of a consecutive series of breast cancer patients who underwent contralateral prophylactic mastectomy with breast reconstruction at Karolinska University Hospital, Stockholm, Sweden between January 1, 1998 and July 1, 2008. For patients’ identification a hospital-based database of primary breast reconstructions at the Department of Reconstructive Plastic Surgery was used, where all patients undergoing CPM with immediate breast reconstruction were entered. Inclusion criteria were women with a personal history of unilateral breast cancer operated on with contralateral risk-reducing mastectomy with breast reconstruction. Exclusion criteria were bilateral prophylactic mastectomy, bilateral mastectomy for bilateral breast cancer. Ninety-one identified breast cancer patients who had undergone CPM with breast reconstruction during the study period were eligible, and thus included. All relevant clinical records from the Departments of General Surgery, Reconstructive Plastic Surgery, Oncology and Family Cancer Clinic
at the Department of Oncology were reviewed. Patients were followed from the date of their initial breast cancer operation until the end for follow-up (July 1, 2010), migration from Stockholm, or death. With the purpose to analyze possible differences and the clinical course of breast reconstruction after CPM, only concurrently performed bilateral breast reconstructions (n=75) were included into the regression and paired comparison analyses. The date of bilateral breast reconstruction (= date of CPM) was chosen as a starting point. The median follow-up time after CPM was 3.9 years (min: 0.5, max: 11.0).

Contralateral prophylactic mastectomy with reconstruction was categorized as “CPM reconstruction”, in contrast to ipsilateral therapeutic mastectomy with reconstruction, which was labeled “TM reconstruction”. Reoperation was an outcome variable assessing morbidity, defined as any surgical procedure under general anesthesia after breast reconstruction, and was documented for each patient and for each breast. The reoperations were classified into three groups: early, implant-related, and corrections for aesthetic reasons. Early reoperation was defined as any postoperative event requiring return to the operating room within 30 days. Implant-related reoperations included implant replacement, pocket revision, implant removal, and secondary reconstruction. Corrections for aesthetic reasons (an operation to improve breast symmetry and cosmesis) included liposuction, lipofilling, abdominal advancement flaps, skin/scars/nipple-areola correction, or combinations.

### 3.2 STUDY II

This is a prospective questionnaire study. All patients with a confirmed personal and family history undergoing CPM (Study I population) were eligible. Before CPM the women had been routinely referred to the psychologist, a member of the multidisciplinary hereditary team (Brandberg et al., 2004). At the end of the consultation, each patient was invited to participate in the questionnaire study. Women agreeing to participate were handed a prepaid envelope together with a questionnaire to be completed at home. Subsequent questionnaires with envelopes were sent 6 and 24 months after CPM. If no response was obtained within one month, one reminder was sent. All questionnaires were coded and stored separately from the keys. Clinical data from a hospital-based database (medical, pathological and surgical records) were collected from patients’ files.

Of ninety-one consecutive breast cancer patients who underwent CPM during the study period, 22 did not have a consultation with the medical psychologist before CPM: twelve women because they underwent CPM in conjunction with breast cancer surgery and ten women due to administrative failure. Of the remaining 69 women invited to participate, 9 did not return any questionnaire. Thus, a total of 60 patients who responded at any of the assessment points were included in the study.

Four validated questionnaires were used in this study. The Short Form-36 Health Survey (SF-36) is a generic HRQoL instrument that includes 36 items, defining eight HRQoL domains: physical functioning, role limitations due to physical problems,
bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, and general health perception (Ware and Sherbourne, 1992). The Swedish version has been validated and normative data for Swedish women have been published (Sullivan et al., 1995).

The Hospital Anxiety and Depression scale, HAD, was originally designed to detect anxiety and depression in somatically ill patients. It contains 14 items, 7 assessing anxiety and 7 assessing depression. Scores range from 0 to 3 for each question, giving the summated score for each scale the range from 0 to 21 (Zigmond and Snaith, 1983). For both anxiety and depression subscales, the summed scores 0-7 represent non-cases (normal), 8-10 possible clinical cases, and 11-21 represent clinical levels of anxiety and depression. The Swedish translation of the HAD scale has been validated against diaries in breast cancer patients (Arving et al., 2008).

The Body Image Scale, BIS, aims to assess the impact of surgery on patients’ self-consciousness, physical and sexual attractiveness, femininity, satisfaction with body and scars, body integrity, and avoidance behavior. The 10-item scale is scored from 0 (not at all) to 3 (very much). The sum of the BIS-items gives an overall score (range 0-30).

The Sexuality Activity Questionnaire, SAQ, includes 10 items assessing sexual activity and divided into three sections: pleasure (desire, enjoyment and satisfaction), discomfort (dryness, pain), and habit (sexual behavior) (Houlston and Peto, 2004). The pleasure section includes 6 items (scores: from 0 to 18); the discomfort section-2 items (scores: from 0 to 6); the habit section- 1 item (scores: from 0 to 3). The sums of six items and two items give overall scores concerning sexual pleasure and discomfort, respectively.

Together with these four questionnaires, study participants received a questionnaire for self-assessment of the cosmetic results of breast reconstruction. The Cosmetic Result Questionnaire was constructed for evaluation of patients’ satisfaction with breast reconstruction. This original questionnaire has not undergone formal validation, but has been used in a number of studies assessing breast reconstruction outcomes (Olson et al., 2004). Women were asked to assess each of the breasts by rating their satisfaction with the size (“Too little”, “Satisfactory”, “Too large”), the shape (from 1 “Very bad” to 7 “Very good”), the softness (“Too soft”, “Satisfactory”, “Too hard”), the scars (from 1 “Very bad” to 7 “Very good”), and the appearance of the nipples (from 1 “Very bad” to 7 “Very good”). One item concerned overall breast sensibility (scored in seven categories from 1 “Very bad” to 7 “Very good”). Finally, patients were asked “Would you recommend this type of operation to another woman in the same situation?” (scored in seven categories from “No, never” to “Yes, absolutely”).
3.3 STUDY III

This is a retrospective cohort study of consecutive patients diagnosed with breast cancer having undergone mastectomy within the Stockholm-Gotland area between 2009 and 2011 and receiving postmastectomy radiotherapy. The National Breast Cancer Register was used for patient identification. Data on type and date of breast cancer surgery, tumor characteristics (laterality, size and lymph nodes involvement) and planned treatment (radiotherapy, chemotherapy, endocrine therapy) were obtained from the register. All patients were further identified in the prospectively maintained hospital-based radiation oncology verification system (ARIA©, Varian Medical Systems). The dates for radiotherapy (start and end), radiotherapy plan (with targets including chest wall or chest wall plus lymph nodes), total dose, number of fractions, boost and bolus (if any), were retrieved from the RT charts in ARIA.

The inclusion criteria were mastectomy as the primary surgery for breast cancer and full course of PMRT to the ipsilateral chest wall +/- regional lymph nodes. Patients were excluded for the following reasons (Figure 12):
1) Missing data in the verification system; when changes in adjuvant treatment plan ruled out PMRT or treatment was received elsewhere. 2) Radiotherapy course with a fractionation different than 2 Gy in 25 fractions; as inclusion of patients treated with hyper- or hypofractionation could affect dosimetric comparisons. 3) Other than 6-MV photons energy; as we aimed to evaluate the 6-MV energy with photons, being the standard for our department, although some patients with a larger breast may have received 15-MV or 18-MV, or a combination of energies for the dose homogeneity. 4) Cancelled, interrupted or changed radiotherapy course, to ensure that all the patients in the study had received RT according to the accepted radiotherapy plans. 5) Radiotherapy to other than the ipsilateral chest wall or chest wall plus lymph nodes target area.

Thus, 237 patients were excluded and the remaining 720 were included into the study. In the patients with immediate breast reconstruction, the implants were placed under total muscular coverage on the chest wall. Three types of implants were used during the study period (Figure 2): type I, temporary expanders with a single lumen and an integrated magnetic port at the center of the implant for postoperative expansion; type II, expandable implants that are designed for a definitive one-stage breast reconstruction. These contain an outer chamber with silicon gel and an inner chamber that may be inflated postoperatively with saline via the remote injection port placed subcutaneously on the chest wall; type III, permanent implants filled with silicon gel with a predefined volume.
Dose Volume Histograms (DVHs), summarizing the 3D dose distribution in 2D format, as well as dose statistics for ipsilateral lung, heart and clinical target volume were retrieved from the system. Ipsilateral lung dosimetry was assessed using minimum, maximum and mean dose to the lung, as well as % of volume receiving 20 Gy ($V_{20\text{Gy}}$). The heart dosimetry was evaluated only in patients with left-sided breast cancer due to the fact that irradiation of the heart in the right-sided plans was negligible. Heart variables included minimum, maximum, mean dose and percent of volume receiving 25 Gy ($V_{25\text{Gy}}$), and NTCP. CTV coverage was defined as percentage of clinical target volume covered by ≥95% of isodose (CTV $V_{95\%}$). In an attempt to take into account patients’ chest wall shape, the following parameters were also considered: transverse diameter (T, internal transverse diameter of thorax), antero-posterior diameter (AP, from the back of the sternum to the front of the vertebra) and hemithorax anteroposterior diameter. Measurements were performed at the isocenter slice of the CT scan or at the mamillary level in patients where the isocenter was placed outside the mamillary level. Chest wall index (CWI) was defined as the ratio between the transverse and the antero-posterior diameter (T/AP) as suggested by (Haller et al., 1987).

3D CT-based radiation treatment planning was performed using the Varian Medical System Platform software (Varian Medical Systems Inc., Palo Alto, USA). Ipsilateral
lung was contoured using auto-outline tool, whereas heart and clinical target volume (CTV) were delineated manually according to local guidelines. CTV was defined as chest wall only (CW) for local radiotherapy plans or chest wall plus lymph nodes, i.e. axillary, infraclavicular and supraclavicular region and upper level internal mammary lymph nodes (IMN), for loco-regional radiotherapy. In patients with IBR, CTV was always delineated comprising the breast implant.

Conventional tangential external-beam radiotherapy with 6-MV photons was used in all cases. Total prescribed dose was 50 Gy in 2 Gy daily fractions. Additional boost dose to the mastectomy scar and/or bolus was utilized in some patients. When CW only was included in the CTV the treatment technique consisted of two 6-MV tangential fields. For those cases where the CTV included the lymph nodes, an isocentric technique was used, consisting of tangential fields covering CW and usually three fields covering the lymph nodes in the supraclavicular fossa and in the axillary regions. Fields-in fields solutions were applied where necessary.

Dose calculations were performed with the Eclipse Treatment Planning System using the Analytical Anisotropic Algorithm, AAA (Varian). The dose was prescribed so that the CTV would be encompassed between 95% and 105% isodoses. According to the local protocols the constraints to the ipsilateral lung was percentage of volume receiving 20 Gy (V20Gy) < 30%, and constraints to the heart included mean dose < 5 Gy and normal tissues complications probability (NTCP) index < 1% (Gagliardi et al., 1996). The clinical protocols for radiotherapy planning were the same during the study period.

3.4 STUDY IV

This is a descriptive retrospective multicenter study of consecutively operated patients with complications of polyacrylamide gel injections with a prospective clinical follow-up evaluation.

All women that presented with complications after PAAG injections for breast augmentation at three teaching hospitals in Ukraine from February 1998 to September 2009 were eligible. The PAAG injections had been performed elsewhere and all patients were self-referred. Patients were retrospectively identified using an operating room logbook where all surgical procedures performed at each of the three departments were registered, including information on patient’s medical chart number, diagnosis, date and type of operation.

Inclusion criteria were patients having undergone revision procedures following PAAG injections. Patients without sufficient medical documentation, i.e. unavailable or incomplete medical or surgical records, were excluded (Figure 13).
Figure 13. Eligible, included and available for clinical follow-up patients in Study IV.

All relevant clinical records from three teaching hospitals in Ukraine were reviewed. A study database was constructed including variables such as date of birth, date of injection, volume of injected gel, injection site, symptoms at presentation, patient’s BMI at debridement operation, dates and types of reoperations. Available socio-demographic data were extracted and stored in a separate electronic database. An introductory letter with an invitation to participate in the clinical follow-up study was sent to the patients together with a prepaid return envelope. If no response was obtained within 1 month, patients were contacted by phone. In addition, all invited patients were offered a free breast ultrasound examination and a consultation with a plastic surgeon. Women were seen in one of the three outpatient clinics between February 2010 and September 2010 by three of the co-authors. The consultation included current medical history, breast inspection, symmetry measurement (sternal notch to nipple, nipple to midline and nipple to submammary fold), as well as breast ultrasonography and photographic documentation.

At follow-up patients were asked to fill in study questionnaires, which included EQ-5D, an aesthetic outcome questionnaire, and a study-specific questionnaire. The EQ-5D questionnaire is a validated and globally used non-disease specific instrument that measures health-related quality of life. It consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). Each of the 5 dimensions in the EQ-5D descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) has three levels: no problems, some problems, and severe problems. EQ-VAS is a vertical visual analogue scale for self-rating of current health-related quality of life, ranging from 0 “worst imaginable health state” to 100 “best imaginable health state” (Cheung et al., 2009).

The aesthetic outcome questionnaire consisted of four structured questions assessing satisfaction with the size, shape, symmetry and sensibility of the breast. Each assessment was scored in seven categories from 1 “Very bad” to 7 “Very good” (Brandberg et al., 1999). Patients were also asked to rate their intensity of pain on a
horizontal scale of 100 mm with descriptors “No pain” and “Very severe pain” at each end (Wewers and Lowe, 1990). Finally, a study-specific questionnaire for guided interview was designed to collect extended socio-demographic data and details about the PAAG injection.

3.5 STATISTICAL METHODS

Study I

Analysis of reoperation risk after bilateral reconstruction was performed using the McNemar’s test for paired proportions. Results are presented as proportions, paired difference with 95% confidence interval (95% CI) and \( p \)-value calculated using the binomial distribution. Difference in the mean number of reoperations was tested using the paired t-test and results are presented as the mean difference together with 95% CI. Reoperation following CPM with bilateral breast reconstruction – as a dichotomous outcome – was analysed using univariate and multivariate logistic regression models. Variables as age, body mass index, radiotherapy, chemotherapy, and endocrine therapy were included into the multivariate regression model to control for potential confounding, assuming that they might be associated with complications. The associations between reoperation and potential categorical risk factors were presented as odds ratios (OR) with 95% CI and \( p \)-value. Reported \( p \)-values from these models refer to the Wald-test.

Study II

All single items in the SF-36 were transformed into the 8 subscales (presented on Figure 5) with scores ranging 0-100 according to the scoring manual (Sullivan et al., 1995). High figures represent higher level of functioning and HRQoL. In the interpretation of the subscale scores, a difference of \( \geq 5 \) points on the 0-100 scale was considered clinically important and defined as clinical cases (Osoba et al., 1998). For BIS subscales presentation, we dichotomized the results into 0 (no problems) and 1-3 (problems, or negative changes). Mean scores for SF-36, HAD, BIS, SAQ at preoperative, 6 and 24 months assessments were analysed using linear regression models. Test for differences between participants and non-participants in clinical and demographic characteristics were performed using Fisher’s exact test.
Study III

Pearson’s chi-square or t-test when appropriate was utilized for assessment of differences in patients with (IBR+, n=162) and without (IBR-, n=558) breast reconstruction.

For the purpose of statistical analysis, the outcome variables were dichotomized as follows: Lung: $V_{20Gy} \leq 30\%$ vs. $V_{20Gy} > 30\%$; Heart: $D_{mean} \leq 5$ Gy vs. $D_{mean} > 5$ Gy, CTV: $V_{95\%} \geq$median vs. $V_{95\%} <$median. In the assessment of heart avoidance, only left-sided radiotherapy plans were used.

Univariate and multivariate regression models were performed to test the association of outcome variables and potential confounders (breast reconstruction, side of RT, CW index). Chest wall (n=236) and chest wall plus lymph nodes (n=484) radiation plans were studied in two separate regression models. The results were presented as odds ratios (OR) with 95% CI and $p$-value. Reported p-values from these models referred to the Wald-test.

Study IV

Descriptive data are presented in tables as number of cases and frequencies, i.e. n (%). Mean values with a range (min–max) or standard deviation (SD) were used when appropriate. EQ-5D was analyzed according to the scoring manual (Cheung et al., 2009). VAS score was measured and reported in millimeters. Breast symmetry was analysed in the paired t-test and presented as a mean difference between distances on the right and left sides. In the aesthetic results questionnaire, satisfaction with the breast characteristics was categorized as “negative” (1–3), “neutral” (4), or “positive” (5–7).

STATA/SE (Version 11.1) for PC and MacOS, StataCorp, TX, USA, was used for all statistical analyses. A two-tailed $p < 0.05$ was considered significant in all statistical tests.

<table>
<thead>
<tr>
<th>Table 2. Statistical methods used in the studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis</td>
</tr>
<tr>
<td>Student’s t-test</td>
</tr>
<tr>
<td>Logistic regression</td>
</tr>
<tr>
<td>Linear regression</td>
</tr>
<tr>
<td>McNemar’s test</td>
</tr>
<tr>
<td>Wald-test</td>
</tr>
<tr>
<td>Fisher’s exact test</td>
</tr>
<tr>
<td>Pearson chi²-test</td>
</tr>
</tbody>
</table>
4 SUMMARY OF RESULTS AND DISCUSSION

4.1 STUDY I. CONTRALATERAL PROPHYLACTIC MASTECTOMY AND BREAST RECONSTRUCTION

In this series of 91 patients undergoing CPM with immediate breast reconstruction, 86 (95%) women were bilaterally reconstructed by the end of follow-up, and no contralateral breast cancer was detected during the median follow-up period of 3.9 years (min: 0.5, max: 11.0 years). Seven patients were diagnosed with distant metastases from their primary breast cancer after the date of CPM; six of these succumbed to breast cancer.

The majority of the patients, 78/91 (86%) had a family history of BC and 36 (40%) of them were found to have a mutation in either BRCA1 or BRCA2. On the prophylactic (CPM) side, nipple-sparing mastectomy with the regrafting of the nipple tip was performed in 65 (72%) of the patients. All women underwent a single-stage breast reconstruction. The majority (n=75, 82%) received concurrent bilateral Br, the remaining 16 (18%) had previously been reconstructed on the TM side and thus received unilateral CPM reconstruction.

The probability and timing for reoperation for all patients (n=91) on the cancer and prophylactic side is presented in Figure 14 (unpublished data).

![Figure 14](image.png)

Figure 14. Probability of reoperation after the cancer side reconstruction (TM Rec) and the prophylactic side reconstruction (CPM Rec) over time, unpaired data.
In the subset of patients with concurrent bilateral BRs (n=75), 52 (69%) permanent expanders, 21 (28%) permanent implants and two (3%) DIEP flaps were used. Overall, 60% required one or more reoperations on any side following CPM with bilateral BR. Median time to reoperation on any side was 9 months (range, 0-47). The risk of reoperation was significantly higher on the cancer side as compared to the prophylactic side (57% vs. 37%, p=0.001). Among the patients who received RT (n=49, 65%), reoperation risk on the cancer side was significantly higher than on the prophylactic side (71% vs. 41%, p=0.0003, data not shown).

In total, 100 reoperations were performed in 75 patients during the follow-up period: 37 interventions on the CPM side and 63 on the TM side. The mean number of reoperations required for completion of CPM and TM reconstruction was 0.49 and 0.84, respectively, with a significant mean difference of 0.35 (95% CI 0.16 – 0.53, p=0.003). The most common indication for reoperation on any side was implant-related as indicated in Table 3.

<table>
<thead>
<tr>
<th>Reoperation</th>
<th>CPM side</th>
<th>TM side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early postoperative reoperations</td>
<td>4 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Implant-related reoperations</td>
<td>21 (28)</td>
<td>44 (59)</td>
</tr>
<tr>
<td>Capsulotomy and implant replacement</td>
<td>10 (13)</td>
<td>37 (49)</td>
</tr>
<tr>
<td>Implant replacement</td>
<td>7 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Implant removal</td>
<td>3 (4)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Secondary reconstruction</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Correction for aesthetic reasons²</td>
<td>12 (16)</td>
<td>17 (23)</td>
</tr>
</tbody>
</table>

Table 3. Description of all reoperations after bilateral breast reconstruction (n=75)

In the regression analysis, radiotherapy was associated with reoperation (OR 4.2, 95% CI 1.3–13.6, p=0.015) after adjustment for age, BMI, chemotherapy, and endocrine therapy (data not shown).

Seven patients had experienced severe implant infection that resulted in unilateral (n=3) or bilateral (n=4) implant removal. Secondary reconstructions were later performed in two patients with unilateral failures whereas the remaining (n=5) received no further breast reconstruction due to personal (n=3) or medical (obesity, n=1; diabetes mellitus, n=1) concerns.

In a similar study that addressed the outcomes of CPM with bilateral BR, the overall probability of reoperation in a selected subset of patients with implant-based reconstruction (n=334) was 31% with no difference between CPM and TM sides (Crosby et al., 2011). These data are not directly comparable with our results as their analysis was performed on a ‘per breast’ basis, irradiated patients were not included and the follow-up period was limited to 13 months. In our study, 65% were irradiated for their primary BC and patients were followed-up for 3.9 years.
Notably, among possible clinical and patients’ characteristics, only radiotherapy was associated with reoperation, and our findings are in line with other studies evaluating an impact of radiotherapy on implant-based breast reconstruction (Krueger et al., 2001; Ascherman et al., 2006). Berry et al. reported radiation to be the greatest risk factor for reoperation among patients with expander/implant reconstruction (n=595), where 59% irradiated patients had complications compared to 28% in the non-irradiated subgroup (Berry et al., 2010).

At our institution, prophylactic mastectomies are offered predominantly to high-risk patients and that fact may explain the limited number of patients in this study despite of the long study period. The patients are thoroughly selected with respect to primary cancer data (risk of relapse) and genetic counseling (estimation of contralateral breast cancer risk) in contrast to some studies reporting CPM performed among the general population of patients at the time of the cancer surgery (Boughey et al., 2010; Crosby et al., 2011). Thus, in practice CPM will not usually take place until two years after primary cancer surgery. In this study, the mean time between breast cancer surgery and contralateral prophylactic mastectomy was 3.3 years. Some of the patients have already been reconstructed on the cancer side when they opted for risk-reducing surgery, whereas the majority received bilateral reconstruction at the time of CPM. The described cohort is heterogeneous due to different treatment scenarios in patients with a personal and family history of breast cancer.

4.2 STUDY II. QUALITY OF LIFE AFTER CONTRALATERAL PROPHYLACTIC MASTECTOMY

The response rate varied from 75% to 82%; 45 (75%) patients responded to the questionnaires before contralateral prophylactic mastectomy, 49 (82%) at the 6-month, and 45 (75%) at the 2-year assessment after CPM.

Health-related quality of life (SF-36)

No statistically significant differences were found between preoperative and postoperative assessments for any of the SF-36 subscales. Two years after CPM, a positive clinical difference (≥5) in social functioning and mental health was found. However, six months after CPM, patients scored lower on physical role, bodily pain and role emotional domains when compared with the preoperative values, which was considered clinically significant (Table 4).

The comparison between patients 2 years after CPM and normative data revealed statistically significant difference in bodily pain subscale favoring the patients (p = 0.007, data not shown).
Anxiety and depression (HAD)

No statistically significant differences between preoperative and postoperative mean levels were found for anxiety or depression (Table 4).

<table>
<thead>
<tr>
<th>Scale and measure</th>
<th>Before CPM (n=42-44)</th>
<th>6 months after CPM (n=45-48)</th>
<th>2 years after CPM (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
</tr>
<tr>
<td>SF-36 Questionnaire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>89.2</td>
<td>85.6 to 92.8</td>
<td>89.0</td>
</tr>
<tr>
<td>Physical role</td>
<td>82.0</td>
<td>72.4 to 91.5</td>
<td>69.3</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>79.8</td>
<td>72.6 to 87.1</td>
<td>72.7</td>
</tr>
<tr>
<td>General health</td>
<td>70.1</td>
<td>63.0 to 77.3</td>
<td>69.6</td>
</tr>
<tr>
<td>Vitality</td>
<td>63.2</td>
<td>56.4 to 70.0</td>
<td>61.1</td>
</tr>
<tr>
<td>Social functioning</td>
<td>81.0</td>
<td>74.0 to 87.9</td>
<td>84.0</td>
</tr>
<tr>
<td>Role emotional</td>
<td>76.7</td>
<td>65.4 to 88.1</td>
<td>71.6</td>
</tr>
<tr>
<td>Mental health</td>
<td>71.4</td>
<td>65.1 to 77.7</td>
<td>72.7</td>
</tr>
<tr>
<td>HAD Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>7.5</td>
<td>6.0 to 9.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Depression</td>
<td>4.0</td>
<td>2.8 to 5.1</td>
<td>3.7</td>
</tr>
</tbody>
</table>

CI confidence interval, CPM contralateral prophylactic mastectomy

Body image (BIS)

The mean BIS overall scores six months and two years postoperatively were 7.8 (95% CI, 6.0 to 9.6) and 7.1 (95% CI, 5.5 to 8.8), respectively, and revealed no statistically significant difference in body image over time. Two years after CPM, more than 50% of the women reported problems with appearance and with the scars, felt less attractive and feminine.

Sexuality (SAQ)

No statistically significant difference was found when preoperative and postoperative scores were compared for pleasure, discomfort and habit subscales. The number of patients who reported an intimate relationship before, 6 months and years after CPM were 37/45 (82%), 36/47 (77%) and 33/42 (79%) respectively.

Patient satisfaction with the cosmetic result of breast reconstruction

Two years postoperatively, of 42/60 responders, 36 (86%) and 33 (79%) were satisfied with the size of CPM and TM breasts, respectively.
Patients scored breast softness as satisfactory in 33 (77%) of the CPM breasts and in 18 (42%) of the TM breasts. Satisfaction with breast shape, nipples, and scars is presented in Figure 15 (unpublished data). Reported overall breast sensibility (n=43) was rated positive in 16 (37%), neutral in 14 (33%) and negative in 23 (54%) patients. Of 39 patients, 32 (82%) responded positively to the question “Would you recommend this type of operation to another woman?”.

Overall, the patients showed a satisfactory HRQoL, that was comparable with the levels found among breast cancer patients who have not undergone CPM (Frost et al., 2005; Geiger et al., 2006; Spear et al., 2008) and similar to women in the general population. Six months after CPM, however, patients scored clinically lower than preoperatively on three SF-36 domains. This could be attributed to ongoing reconstruction-related procedures, as two years postoperatively the scores of these HRQoL domains were consistent with the preoperative levels.

The levels of anxiety and depression did not change over time. In a prospective follow-up study of women with high hereditary risk for breast cancer who had undergone bilateral prophylactic mastectomy, anxiety appeared to decrease after BPM (Brandberg et al., 2008). The postoperative levels of anxiety found in the
present study correspond to figures among breast cancer patients (Arving et al., 2008). The fact that the women in the present study had experienced a breast cancer diagnosis might have had a larger impact on their level of anxiety than that of getting a new breast cancer.

Satisfaction with body image after CPM did not change over time, but varied among the patients. More than half of the responders reported problems/dissatisfaction with their body, appearance, scars, femininity and attractiveness 2 years after CPM. Similar findings were found in the group of patients undergoing BPM, where some women reported problems in body image and negative changes in sexuality after the operation (Brandberg et al., 2008).

Finally, the tendency that women were less satisfied with the specific aesthetic outcomes on the cancer side (compared to the prophylactic side) may be related to the received irradiation and unanticipated reoperations on the ipsilateral side (findings of Study I).

This study is relatively small as it suffers from a limited number of participants (n=60) and moderate response rate (75-82%). The strength of the study lies in its prospective design. Patients were assessed with well-known validated instruments preoperatively, 6 months and 2 years after CPM. As CPM was conducted as a delayed procedure, we were able to evaluate the psychosocial implications of CPM separately from the cancer treatment. The results are also supported by other studies assessing HRQoL in patients after risk reducing mastectomy with breast reconstruction (Gahm et al., 2008; Isern et al., 2008).

4.3 STUDY III. POSTMASTECTOMY RADIOTHERAPY AND BREAST IMPLANTS

This study shows that in patients undergoing postmastectomy radiotherapy, the presence of breast implants is not associated with increased doses to risk organs (ipsilateral lung and heart) or decreased coverage of CTV. Dosimetric and anthropometric characteristics for IBR+ and IBR- patients stratified for radiotherapy plan are presented in Table 5.

Overall, clinical target volume was larger in IBR+ compared to IBR- both for chest wall only (637 vs. 446 cm³, p<0.001) and chest wall plus lymph nodes (1094 vs. 772 cm³, p<0.001) radiation targets.

In IBR+ patients, CTV mean dose and CTV V 105% were lower (100.1 vs. 100.8%, p=0.04 and 11.5 vs. 13.1%, p=0.03, respectively). There was a difference in chest wall shape, i.e. chest wall index was statistically significantly lower in IBR- group (2.3 vs. 2.5, p<0.001).

In the chest wall subset, IBR+ patients were significantly different from IBR- with regards to the lung maximum dose (52.0 vs. 51.4, p=0.01) and CTV V 105% (11.1 vs. 15.3%, p=0.006). Assessing the subset of patients with chest wall plus lymph nodes target, mean and maximum doses to the ipsilateral lung were lower in IBR+ patients (13.8 vs. 14.4 Gy, p=0.02 and 51.5 vs. 51.9 Gy, p<0.002, respectively).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=236)</th>
<th>IBR+ (n=80)</th>
<th>IBR- (n=156)</th>
<th>P-value¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume, cm³ [SD]</td>
<td>1426.5 [320.0]</td>
<td>1458.6 [318.8]</td>
<td>1410.1 [320.3]</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean dose, Gy [SD]</td>
<td>8.8 [3.7]</td>
<td>8.9 [5.2]</td>
<td>8.8 [2.7]</td>
<td>0.87</td>
</tr>
<tr>
<td>Minimum dose, Gy</td>
<td>0.3</td>
<td>0.4</td>
<td>0.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Maximum dose, Gy</td>
<td>51.6</td>
<td>52.0</td>
<td>51.4</td>
<td>0.001</td>
</tr>
<tr>
<td>$V_{20Gy}$, % [SD]</td>
<td>16.0 [5.8]</td>
<td>15.5 [5.7]</td>
<td>16.2 [5.9]</td>
<td>0.38</td>
</tr>
<tr>
<td>Heart‡</td>
<td>n=484</td>
<td>n=82</td>
<td>n=402</td>
<td></td>
</tr>
<tr>
<td>Volume, cm³ [SD]</td>
<td>513.6 [134.6]</td>
<td>513.9 [115.5]</td>
<td>512.6 [142.7]</td>
<td>0.91</td>
</tr>
<tr>
<td>Mean dose, Gy [SD]</td>
<td>3.3 [1.8]</td>
<td>3.0 [0.9]</td>
<td>3.4 [2.1]</td>
<td>0.39</td>
</tr>
<tr>
<td>Minimum dose, Gy</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Maximum dose, Gy</td>
<td>48.4</td>
<td>48.7</td>
<td>48.4</td>
<td>0.79</td>
</tr>
<tr>
<td>$V_{25Gy}$, % [SD]</td>
<td>3.6 [2.3]</td>
<td>3.1 [1.7]</td>
<td>3.8 [2.3]</td>
<td>0.09</td>
</tr>
<tr>
<td>CTV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume, cm³ [SD]</td>
<td>5108 [273.6]</td>
<td>6365 [273.6]</td>
<td>4464 [261.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean dose, %</td>
<td>100.9 [7.5]</td>
<td>100.5 [1.7]</td>
<td>101.2 [9.2]</td>
<td>0.49</td>
</tr>
<tr>
<td>$V_{95%}$, %</td>
<td>91.5 [7.5]</td>
<td>91.7 [5.1]</td>
<td>91.4 [8.5]</td>
<td>0.81</td>
</tr>
<tr>
<td>$V_{105%}$, %</td>
<td>13.9 [11.2]</td>
<td>11.8 [8.3]</td>
<td>15.3 [12.2]</td>
<td>0.006</td>
</tr>
<tr>
<td>Chest wall index †</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse diameter, cm [SD]</td>
<td>23.5 [1.4]</td>
<td>23.7 [1.2]</td>
<td>23.5 [1.4]</td>
<td>0.35</td>
</tr>
<tr>
<td>Anteroposterior diameter, cm [SD]</td>
<td>10.1 [1.6]</td>
<td>9.6 [1.4]</td>
<td>10.4 [1.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest wall index [SD]</td>
<td>2.4 [0.4]</td>
<td>2.5 [0.4]</td>
<td>2.3 [0.4]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* All numbers in the rows indicate mean values for the corresponding columns; [SD] standard deviation

CTV indicates clinical target volume; $V_{95\%}$ and $V_{105\%}$, volume irradiated with 95% and 105% of isodose; $V_{20Gy}$ and $V_{25Gy}$, volume irradiated with 20 Gy and 25 Gy.

‡ Calculated for left-sided plans only

§ Calculated for 45 IBR- and 17 IBR+ patients in chest wall subgroup; 121 IBR- and 19 IBR+ in chest wall plus lymph nodes subgroup

¶ Student’s independent t-test

† Measured at isocenter tomography slide or mammillary level
The univariate analyses revealed no association between breast implant reconstruction and dosimetric characteristics neither in chest wall nor chest wall plus lymph nodes subset (data not shown). Corresponding results from the multivariate analyses are shown in Table 6.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Covariate</th>
<th>Chest wall (n=236)</th>
<th>Chest wall plus lymph nodes (n=484)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Lung V&lt;sub&gt;20Gy&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBR- vs. IBR+</td>
<td>1.6 (0.4 to 6.4)</td>
<td>0.52</td>
<td>0.6 (0.4 to 1.0)</td>
</tr>
<tr>
<td>Right vs. Left</td>
<td>1.3 (0.3 to 5.1)</td>
<td>0.67</td>
<td>1.1 (0.8 to 1.7)</td>
</tr>
<tr>
<td>CWi ≤median vs. CWi&gt;median</td>
<td>1.1 (0.3 to 4.4)</td>
<td>0.88</td>
<td>1.4 (1.0 to 2.0)</td>
</tr>
<tr>
<td>Heart D&lt;sub&gt;mean&lt;/sub&gt;*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBR- vs. IBR+</td>
<td>-</td>
<td></td>
<td>1.1 (0.4 to 3.0)</td>
</tr>
<tr>
<td>Right vs. Left</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>CWi ≤median vs. CWi&gt;median</td>
<td>1.0 (0.1 to 7.9)</td>
<td>0.98</td>
<td>1.2 (0.6 to 2.7)</td>
</tr>
<tr>
<td>CTV V&lt;sub&gt;95%&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBR- vs. IBR+</td>
<td>0.9 (0.5 to 1.6)</td>
<td>0.78</td>
<td>0.8 (0.5 to 1.3)</td>
</tr>
<tr>
<td>Right vs. Left</td>
<td>0.8 (0.5 to 1.4)</td>
<td>0.48</td>
<td>1.1 (0.8 to 1.6)</td>
</tr>
<tr>
<td>CWi ≤median vs. CWi&gt;median</td>
<td>1.6 (0.9 to 2.8)</td>
<td>0.08</td>
<td>1.0 (0.7 to 1.4)</td>
</tr>
</tbody>
</table>

IBR immediate breast reconstruction, CWi chest wall index, OR odds ratio, CI confidence interval.
Lung V<sub>20Gy</sub>, volume of ipsilateral lung tissue irradiated with 20 Gy (strata: ≤30% vs. >30%); Heart D<sub>mean</sub>, mean dose delivered to heart (strata: ≤5 Gy vs. >5 Gy); CTV V<sub>95%</sub>, percent of clinical target volume irradiated with ≥ 95% of isodose (strata: ≥median vs. <median).
*analyzed for patients with left-sided radiation plans: chest wall subset (n=82), chest wall plus lymph nodes (n=250)
# no patients in IBR+ subset received >5 Gy

In the IBR+ subgroup analysis we found no correlation between the type of implants and the three outcome dosimetric variables (data not shown). Time from mastectomy to radiotherapy start among patients with temporary expanders permanent expanders, permanent implants, and no reconstruction was 4.5, 4.1, 4.8, and 3.8 months, respectively with no statistically significant difference (data not shown).

A recent case-control study (Ohri et al., 2012) compared 196 patients having implant-based IBR with 51 matched controls without IBR, concluding that having an implant was associated with non-superior doses to heart, lower doses to lung, and excellent chest wall coverage. Notably, planning target volume, ipsilateral lung and heart structures were delineated for study purposes de novo. Moreover, the target volume for IBR- subset was not delineated. The interpretation and generalization of the study results is difficult due to the fact that different radiation techniques were utilized in the two groups.
4.4 STUDY IV. COMPLICATIONS AFTER POLYACRYLAMIDE INJECTIONS

This study found that PAAG injections for breast augmentation could lead to severe complications necessitating multiple debridement operations and sometimes partial or total mastectomy with breast reconstruction.

Complications following PAAG injections occurred early and late. The majority of the patients presented late, with a mean time from injection to debridement of 6 years. Their mean age at the debridement operation was 35 years (range 20-56). At presentation 93 (88%) had had bilateral PAAG injections, and the total number of breasts with PAAG comprised 199. The mean volume of injected PAAG reported by 50 patients was 230 ml/breast (range 50-400).

Patients' symptoms at presentation were: pain 85 (80%), breast hardening 79 (74%), breast deformity 77 (73%), lumps 57 (54%), gel migration 39 (37%), fistulas 17 (16%), and gel leakage 12 (11%). In most cases, gel deposits were mostly located in front of the pectoralis muscle.

The gel was extracted through the open wound using a suction system with further rinsing with saline or furacillin® solution. Submammary incisions were used in 88 (83%) patients, as the method of choice allowing both wide tissue dissection and better visualization. When necessary, additional incisions were required to remove migrated gel (Figure 16) or to excise the fistulas.

Figure 16. Left: patient with medial and caudal gel migration. Right: patient with bilateral caudal gel migration.

Photography: D. Unukovych
Breast reconstruction had to be performed in the majority (72%) of cases (Table 7). The skin envelope during the debridement interventions could be preserved in all cases, which made reconstruction with implants possible (Figure 17). Permanent implants with a mean volume of 320 ml (range 190-440) were used in all cases of breast reconstruction. When possible, implants were placed under the pectoralis major muscle.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of primary debridement procedure</td>
<td></td>
</tr>
<tr>
<td>PAAG removal alone</td>
<td>107 (54)</td>
</tr>
<tr>
<td>+ partial mastectomy</td>
<td>65 (33)</td>
</tr>
<tr>
<td>+ partial mastectomy/pectoralis resection</td>
<td>12 (6)</td>
</tr>
<tr>
<td>+ subcutaneous mastectomy</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Incisions</td>
<td></td>
</tr>
<tr>
<td>Submammary only</td>
<td>165 (83)</td>
</tr>
<tr>
<td>Periareolar only</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Submammary + periareolar</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Extracted PAAG, ml/breast (n = 77)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>205 (76)</td>
</tr>
<tr>
<td>50-200</td>
<td>50 (65)</td>
</tr>
<tr>
<td>200-400</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Implant reconstruction</td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>86 (43)</td>
</tr>
<tr>
<td>Delayed</td>
<td>58 (29)</td>
</tr>
<tr>
<td>No reconstruction</td>
<td>55 (28)</td>
</tr>
</tbody>
</table>

Forty-eight (45%) patients required reoperation following the primary debridement operation: 15 (14%) one, 26 (24%) two, and 7 (7%) three or more reoperations. Apart from delayed breast reconstruction, reoperations comprised gel-related revision surgeries as well as implant related interventions.

Forty-five (42%) women were available for the clinical follow-up 4.6 years (range, 1.2–12.0) after the gel removal. At the follow-up, the majority of respondents (86%) were satisfied with the breast size, whereas items like breast softness, symmetry, sensitivity, and shape were rated positively by 64, 65, 69, and 54%, respectively.

Although no statistically significant difference between right and left side was found (data not shown), 15 (54%) patients had ≥1 cm difference at any of the 3 points of measure.

Assessing breast-related pain intensity, 15 (41%) reported “no pain” and the median score for the remaining women was 3 mm on the 100-mm scale indicating mild pain.

The EQ-5D questionnaire was answered by 37 patients. The EQ-5D self-report questionnaire revealed that 95%, 97% and 100% of the patients had no problems with usual activities, mobility and self-care respectively. Anxiety/depression and pain/discomfort dimensions were reported as problematic by 32% and 19% respectively. Mean score of the subjective evaluation of HRQoL on EQ-5D VAS was 80 (range 50-100).
Despite repeated interventions, image detected deposits of PAAG were still visible at follow-up, although not symptomatic. Freely injected biomaterials make breast imaging difficult whereby a breast malignancy could potentially be missed. There is no information whether a breast cancer diagnosis has been postponed in patients with PAAG injections. PAAG injected women tend to be in an age category where breast cancer is less prevalent. However, if gel remnants are still present this may challenge future breast imaging. Recently published case-reports also describe cases of breast cancer in women after PAAG injection assuming a possible association (Xiao and Liu, 2008; Abdallah et al., 2009; Cheng et al., 2009).
5 CONCLUDING REMARKS

5.1 SUMMARY OF MAJOR FINDINGS

• Contralateral prophylactic mastectomy with breast reconstruction in patients with a personal and family history of breast cancer is a complex procedure, and more than half of the patients require at least one reconstruction-related reoperation. The clinical course after CPM with bilateral breast reconstruction is predominantly affected by reoperations on the cancer side and given radiotherapy is associated with the risk of reoperation.

• Breast cancer patients with a family history undergoing CPM report a satisfactory HRQoL and few problems postoperatively. No changes in HRQoL, sexuality, anxiety or depression are observed after CPM, although some aspects of body image appear to be affected. Two years postoperatively, patients report high satisfaction with the operation, but the cosmetic outcomes on the cancer side are generally rated lower than those on the prophylactic side.

• In patients receiving postmastectomy radiotherapy, the presence of breast implants has no impact on doses to ipsilateral lung, heart, and clinical target volume when comparing patients with and without breast reconstruction.

• Breast augmentation with polyacrylamide gel biomaterial may lead to severe complications necessitating multiple debridement operations and often breast reconstruction. Despite surgical interventions gel remnants are still found on subsequent breast imaging. Public awareness of the safety of injectables for breast augmentation is warranted.

5.2 FUTURE PERSPECTIVES

Contralateral prophylactic mastectomy

The general increase of risk-reducing surgery and prophylactic mastectomies in particular warrants more studies of higher evidence. Better understanding of the genetic nature of BC as well as other risk factors could possibly facilitate patient selection for risk-reducing surgery. Further, controlled clinical trials with randomization to CPM and no CPM patient groups and longer follow up are desirable
for understanding the actual risk-reduction, especially, in high-risk patients. However, balancing ethical considerations and appropriate study design seem a complex and difficult task.

The optimal timing of CPM and breast reconstruction in patients with a personal and family history is controversial and would require multicenter evaluation with a large and representative sample of patients, where issues as type of reconstruction and radiotherapy should be considered.

From a surgical perspective, guidelines for management of patients opting for CPM with breast reconstruction are highly demanded. The implications of CPM to health-related quality of life and psychosocial aspects should be studied in larger prospective studies with the use of validated questionnaires controlling for important clinical variables such as type of reconstruction, radiotherapy, complications, and reoperations.

Accurate understanding of patients’ emotional and psychosocial state before and after breast reconstruction is needed for counseling, patient selection and effective clinical management. Therefore, development and validation of specific instruments to assess patient-reported outcomes is necessary.

Postmastectomy radiotherapy and breast reconstruction

The knowledge in the literature is insufficient to suggest an optimal timing for breast reconstruction in patients who are anticipated to receive radiotherapy. The possible effects of RT on the course of IBR with different prosthetic devices are not studied in detail. Most of the studies are heterogeneous, have a retrospective design and the interpretation of results is equivocal due to the variety of radiotherapy guidelines and breast reconstruction techniques. This should be addressed in prospective studies with randomization according to reconstruction type (implant vs. autologous tissue) and timing (immediate vs. delayed).

There is lack of evidence whether implants impact postmastectomy radiotherapy in terms of radiotherapy planning and local tumor control, and which type of implant to choose for patients requiring radiotherapy. Large multicenter studies with multivariate analyses and longer follow up can address these unanswered issues. In particular, the radiotherapy target area in patients with implants should be assessed in details considering the area outside implants (i.e. CTV minus implant). Finally, dosimetric evaluation of patients with temporary expanders with integrated magnets should be assessed.

Biomaterials for breast injections and complications

Breast injections with polyacrylamide-based gels are prohibited in most countries nowadays, but women with complications and unfavorable results from such injections may still present in the future.

Due to the fact that biomaterials are used predominantly in private settings, the real magnitude of injections and post injection problems remains unclear. The gel may
also cause diagnostic dilemmas in radiologic evaluation of the breast, even in patients with no complications. Further, several reports describe cases of breast cancer following the injection of PAAG, although no direct link was shown. The difficulty to remove injected gel makes these procedures irreversible. In the light of increasing popularity of other injectable biomaterials (e.g. gels based on hyaluronic acid) clinical trials and assessment of long-term results are much needed.
OLIKA ASPEKTER AV BRÖSTREKONSTUKTION

Riskförminskande bröstoperation, strålbehandling efter bröstoperation, och komplikationer efter bröstförstoringar med gelinsprutning

Möjligheten till bröstrekonstruktion (återuppbyggnad av bröstet) har haft en gynnsam effekt på det kosmetiska och funktionella resultatet för kvinnor med bröstcancer. Bröstrekonstruktion ingår i den kirurgiska behandlingen när hela bröstkörteln avlägsnas (mastektomi). Det är visat att bröstrekonstruktion också bidrar till förbättrad livskvalitet. En icke traditionell metod för bröstförstoring är fri insprutning av en gel s.k. polyakrylamidgel. Denna gel kan ge upphov till svåra komplikationer från smärta till gelansamlingar och fistelbildning vilket kräver olika kirurgiska ingrepp.

Syftet med avhandlingen var att belysa olika aspekter av bröstrekonstruktion. Avhandlingen utvärderar dels konsekvenser av bröstrekonstruktion med utgångspunkt från patienter som opererats för bröstcancer och sedan genomgått förebyggande bröstkirurgi av det friska bröstet (kontralateral profylaktisk mastektomi) med rekonstruktion. Vidare studeras hur stråldoser till riskorgan dvs. hjärta och lunga fördelar sig hos patienter som får bröstkorgsbestrålning på den canceropererade sidan med och utan implantat. Slutligen studeras konsekvenser av bröstförstoring med gel och de komplikationer som uppstått och behandlats i ett stort patientmaterial i Ukraina.


I delstudie II studerades hur livskvalitet, ångest, depression, kroppsuppfattning, och sexualitet förändrades av KPM. Under studieperioden 1998-2008 deltog 60 kvinnor, som besvarade fyra väl utvärderade frågeformulär före operationen, 6 månader och 2 år efter operationen. Inga negativa förändringar i livskvalitet påvisades. Två år efter operationen var kvinnornas livskvalitet i nivå med en svensk kontrollgrupp friska kvinnor. Ett antal specifika aspekter avseende kroppsuppfattning (t.ex. attraktivitet,
femininitet, ärr) upplevdes som problematiska efter KPM. Denna information bör delgas patienter där KPM planeras.


Delstudie IV belyser komplikationer efter bröstförstoring med polyakrylamidgelnjektion hos 106 kvinnor. Komplikationer uppstod i snitt 6 år efter gelinsprutningen då kvinnorna sökte sjukvård på grund av olika symptom, som t.ex. smärta (80%), bröstdeformerings (73%), knöl (54%), och gel migration (37%). Kvinnorna opererades vid tre universitetssjukhus i Ukraina. I samtliga fall avlägsnades all tillgänglig gel genom olika kirurgiska ingrepp där både delar av bröstvävnaden togs bort (39%) eller som i ett mindre antal fall hela bröstkörteln avlägsnades (7%). I majoriteten av alla fall (72%) krävdes en bröstrekonstruktion med implantat för att återställa bröstformen. En allmän medvetenhet om de ogynnsamma effekterna av injektionsbehandling för bröstförstoring är önskvärd.
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