

**OBJECTIVE DECISION MAKING BETWEEN CONVENTIONAL AND
ONCOPLASTIC BREAST-CONSERVING SURGERY OR
MASTECTOMY WITH IMMEDIATE BREAST RECONSTRUCTION**

Ph.D. Thesis

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Objective decision making between conventional and oncoplastic breast-conserving surgery or mastectomy with immediate breast reconstruction

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LIST OF ABBREVIATIONS

ADM: Acellular dermal matrix

AJCC: American Joint Committee on
Cancer

ALND: Axillary lymph node dissection

ASM: areola-sparing mastectomy

BCS: breast-conserving surgery

BCT: breast-conserving therapy

BCTOS: Breast Cancer Treatment
Outcome Scale

BCCT.core: Breast Cancer Conservative
Treatment-cosmetic results

BMI: body mass index

BRCA: breast cancer gene

BR: breast reconstruction

CT: computed tomography

DBR: delayed breast reconstruction

DCIS: ductal carcinoma in situ

D-DBR: delayed-delayed breast
reconstruction

D-IBR: delayed-immediate breast
reconstruction

DTI: direct-to-implant

EORTC: European Organisation for
Research and Treatment of Cancer

ER: estrogen receptor

HER2: human epidermal growth factor
receptor 2

IBR: immediate breast reconstruction

IMF: Inframammary fold

LD: latissimus dorsi

LMWH: low-molecular-weight heparin

LR: local recurrence

DM: distant metastasis

M: mastectomy

MRI: magnetic resonance imaging

MRM: modified radical mastectomy

NAC: nipple-areola complex

NIO: National Institute of Oncology

NCCN: National Comprehensive Cancer
Network

NSABP: National Surgical Adjuvant
Breast and Bowel Project

NICE: National Institute for Health and
Clinical Excellence

NSM: nipple-sparing mastectomy

OPS: oncoplastic surgery

PR: progesterone receptor

ROC: receiver operating characteristic

RT: radiotherapy

SLNB: sentinel lymph node biopsy

SM: standard mastectomy

SSM: skin-sparing mastectomy

ST.: stage

TNM: Tumor node metastasis

TRAM: transverse rectus abdominis
myocutaneous

UH: ultrasound

UK: United Kingdom

US: United States of America

WBRT: whole breast radiation therapy

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1. Introduction

Breast cancer is the most common malignant disease in women, with a gradually increasing incidence, while mortality is decreasing nowadays. The Hungarian National Cancer Registry recorded nearly 7,900 new cases of breast cancer in women, with more than 2,100 deaths in 2014.¹

1.1. Advances in breast surgery

William Halsted introduced radical mastectomy including resection of the breast and its underlying pectoralis major muscle with level III lymphadenectomy to mechanically treat all stages of breast cancer at the end of the 19th century. In 1972 Madden described the modified radical mastectomy preserving both pectoral muscles with level I-II axillary lymph node dissection (ALND).^{2,3}

The prospective, randomized studies of Veronesi and Fisher confirmed that organ-sparing surgery along with adjuvant radiotherapy (RT) - in case of microscopically negative surgical margins - could provide equivalent overall survival compared to mastectomy, in early stage breast cancer.^{4,5} The Milan I study confirmed the long-term oncological safety of quadrantectomy⁴, and subsequently, the National Surgical Adjuvant Breast and Bowel Project (NSABP) 06 confirmed the same effect of wide-excision (lumpectomy).⁶

The improved understanding of tumour biology in the 1980s and 1990s brought a paradigm shift: ultra-radical breast surgeries were abandoned, and breast cancer began to be considered a systematic disease, based on multidisciplinary and scientific evidence (so-called evidence-based medicine).^{7,8} Breast-conserving surgery (BCS) and adjuvant whole-breast radiotherapy (WBRT) have become the gold standard for the vast majority of patients with early-stage breast cancer.^{9,10}

The systematic theory was also very relevant in the setting of sentinel lymph node biopsy (SLNB) as it was based on the hypothesis that the lymphatics follow the anatomical pathway (i.e., from level I to II and finally to level III). SLNB by radio colloid method was first reported in 1993 by Krag et al.¹¹ The concept of SLNB in breast cancer was introduced in the 1990s by Giuliano et al, who in 1994 published the first study using the blue dye method for axillary staging in breast cancer patients. A 10-year follow-up of these patients showed SLNB to be a safe alternative to ALND, and SLNB became the gold standard

treatment for clinically node-negative breast cancer.¹²⁻¹⁴

As a result of population screening programmes and developments in diagnostics, breast cancer is increasingly diagnosed at an early stage (ST. 0-II.), which facilitates the possibility of organ-preservation; currently with an average rate of 70%.^{6,8}

Early detection has brought patients the hope of full recovery, which is supported by increased knowledge of the molecular background of breast cancer and developments in histology and radio-and drug therapy.¹⁵ Oncologic developments in the last 30 years have increased the five-year survival rate by 30% (from 52% to 85.1%) in complex and multidisciplinary care.¹⁵⁻¹⁷

1.2. The era of modern breast surgery

Currently, with the possibility of breast conservation due to oncologic developments, demand for surgeries that also provide satisfactory aesthetic results has increased in women with good prognosis, who express the desire to preserve their femininity.¹⁸

Generally, fair to poor cosmetic outcomes following conservative BCS and WBRT are observed in as many as one-third of treated cases (**Figure 1.**) resulting in decreased quality of life for the patients.¹⁹⁻²³

The main goal of BCS would be the resection of the tumor with adequate surgical margins while achieving a satisfactory cosmetic outcome and preserving glandular function. It is well known that good aesthetics have been associated with better psychological recovery and improved quality of life, which has become more important as the improvements in treatments of breast cancer have led to longer survival of the breast cancer patients.^{15,18 24-29}

The main factor influencing breast deformities following conventional BCS is the large volume of the resected specimen relative to the total breast volume producing asymmetry, retraction, and volume changes in the breast as well as fibrosis of the open cavity during healing. The location of the excision in the different breast quadrants further increases the correlation between the resected volume and a poor cosmetic outcome. The inner quadrants are well known for being more sensitive than the outer upper quadrants to the same excised volume.¹⁹⁻²³



Figure 1. Pictures illustrating significant defects of the lower- inner quadrants of the breast followed by the conventional BCS in the 4th week

There is no consensus in the current literature regarding the maximum removable volume; however, a breast volume loss of over 20% generally leads to significant defects of the breast, although lower percentage volumes have been reported to do so as well.³⁰⁻³²

The importance of the excised breast volume in BCS can be readily understood if the excised specimen is imagined as a sphere after a wide excision (according to the NSABP B06 study) and as a cylinder after a quadrantectomy (according to the Milan I study). Accordingly, the resected volumes are easily calculated by the Cavalieri formula ($4r^3\pi/3$) and the Archimede's formula ($V_{\text{cylinder}}:V_{\text{sphere}}=3:2$).^{33,34,4,6} The calculations show that even for T2 tumors, the average resected breast volume is 50-100 ccm, which equals 20-25% of the volume of an average breast of 350-450 ccm³⁵ (**Table 1.**)

Tumor diameter (cm)	Tumor volume (cm ³)	Specimen volume (cm ³) (wide excision with 1 cm margin)	Specimen volume (cm ³) (quadrantectomy with 2 cm margin)
1	0.52	14.1	21.1
2	4.2	33.5	50.25
3	14	65	97
4	33.5	113	169.5
5	65.4	141	269.25

Table 1. The correlation between tumor diameter and the excised volume of the specimen in wide excision or quadrantectomy of different tumor sizes ^{7,18}

With improved understanding of the molecular background of breast cancer and the development of oncologic breast surgery, concurrent advances in reconstructive plastic surgery were made. ^{18,36-39} (Table 2.)

Oncological advances in breast surgery			Advances in breast reconstruction		
1898	W. Halsted	radical mastectomy	1957	Gilles Millard	breast reduction mammoplasty
1965	Madden	modified radical mastectomy	1960	Strömbeck	horizontal dermoglandular flap
			1961	T. Cronin F. Gerow	invention of silicone implants
			1962	Pitanguy	superiorly pedicled dermoglandular flap
			1970	Benelli	periareolar mammoplasty
			1974	T. Skoog	laterally pedicled dermoglandular flap
1981	Veronesi	breast-conserving therapy (BCT)	1976	Olivari	musculus latissimus dorsi (LD) flap*
1985	Fisher	BCT	1982	C. Hartrampf	transverse rectus abdominus myocutaneous (TRAM) flap**
1991	Bryant A. Toth	skin-sparing mastectomy (SSM)	1982	Radovan, Austad	tissue expanders in breast reconstruction (BR)
1993	W. Audretsch	oncoplastic breast surgery (OPS)	1994	M. Lejour	vertical mammoplasty
			1994	R. Allen	deep inferior epigastric perforator (DIEP) flap***
1994	Giuliano	SLNB in breast cancer	1999	P. Blondeel	DIEP flap in Europe
2000	A. Losken M. Hamdi S. Spear P. Maxwell W. Audretsch A. Grisotti M. Nava	OPS, SSM, nipple-sparing mastectomy (NSM), IBR techniques	2000	S. Coleman G. Rigotti R. Khouri N. Pallua G. Magalon	autologous fat transfer
			2004	Kronowitz	delayed-immediate BR (D-IBR) with tissue expander

Table 2. Historical advances in oncological and reconstructive surgery of the breast

***LD flap:** pedicled, latissimus dorsi myocutaneous flap used in autologous BR based on thoracodorsal vessels

****TRAM flap:** pedicled, transverse rectus abdominis myocutaneous flap used in autologous BR based on the perforators of superior epigastric vessels

*****DIEP flap:** free, deep inferior epigastric perforator flap used in BR based on the perforators of inferior epigastric vessels

1.3. Oncoplastic breast surgery

A sophisticated, organ-preserving breast surgery has developed in the last decade to eliminate the disadvantages of the significant excision in relation to the volume of the breast, and those of the conventional BCSes mentioned earlier, that was named Werner Audretsch oncoplastic breast surgery (OPS).⁴⁰ These surgical techniques are able to achieve the same or improved final result than the initial aesthetic value was while providing the oncological radicality. OPS procedures have to be personalized according to the volume, shape, form and the quality of the skin of the breasts, furthermore the location of the tumor, the tumor-to-breast volume ratio and patient preference.^{7,41,42}

According to the current literature, OPS procedures can provide oncologic safety, with low morbidity and good or excellent aesthetic outcomes.⁴³⁻⁴⁹ It is essential to know that high level evidence is necessary to obtain more generalizable results regarding the oncological and cosmetic outcomes of OPS procedures.

OPS includes the simultaneous correction of the defects of partial mastectomy based on the principles of reconstructive plastic surgery, contralateral breast symmetrization surgeries and immediate BR (IBR) after mastectomy in wider sense.^{18,50,51}

The base of the OPS is that it fills the cavity left after the radical elimination of the tumor by mobilizing and transpositioning the surrounding gland pillars (volume displacement), using the ptosis of the breast, in overall narrowing the basic diameter, re-creating the “footprint” of the breast and repositioning the nipple-areola complex (NAC).

These surgical techniques are modifications of sophisticated plastic surgical mastopexies based on the substructural, vascular supply of the breast (**Figure 2.**)^{18,41,50-52}

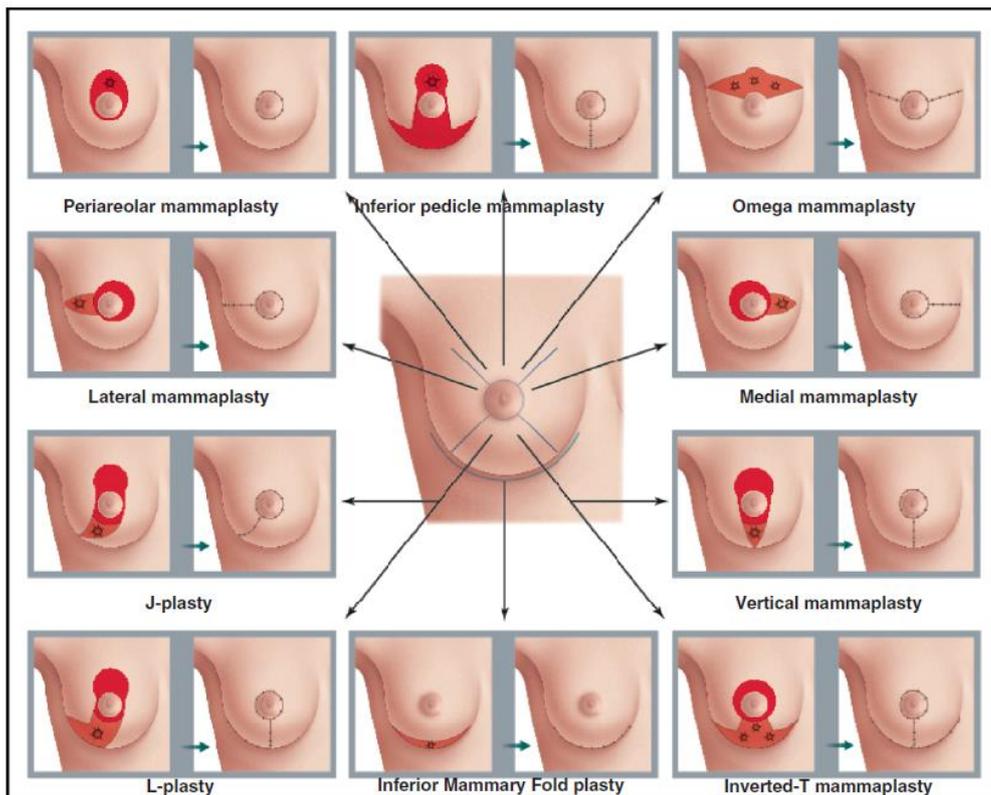


Figure 2. Illustration of the various "volume displacement" OPS techniques in different subregions of the breast based on tumor location ⁵²

Another category of OPS involves volume replacement with local (e.g., thoracoepigastric flap), neighbouring (e.g., LD flap) or distant flaps (e.g., free flaps). ^{7,41}

Presently, nearly 70% of breast cancer cases are eligible for BCS; however, the number of BCS procedures has slightly declined over the last decade. ⁵³⁻⁵⁶ Kummerow et al found that among 1.2 million women with early-stage breast cancer in the United States (US), the proportion of BCS-eligible women who underwent mastectomy increased from 34.3% in 1998 to 37.8% in 2011. ⁵⁴

1.4. Mastectomy and immediate breast reconstruction

Up to 30% of women may present residual deformity requiring surgical correction after BCT, and a number of women may need mastectomy after initial BCT because incomplete resection margins or local recurrence (LR), not to mention the expensive preoperative marking techniques of the non-palpable tumors, the intraoperative histological or radiological examinations of the specimen and logistically complicated absolute indication for adjuvant WBRT.¹⁹⁻²³ The above-detailed OPS techniques allow maximal radicality in BCS resulting in acceptable or excellent cosmetic outcomes mainly in patients with moderate- or large-sized breasts.^{18,43,52}

However, according to the current literature, 30-40% of patients still undergo mastectomy due to one or more of the following: unfavourable tumour location, unfavourable breast-to-tumour volume ratio in patients with small-to-intermediate sized breasts, multifocal disease, extensive ductal carcinoma in situ, inability of adequate re-excision due to positive surgical margine, rejection of RT, and patient preference (e.g., based on whether they carry the BRCA1/2 gene mutation). Furthermore, a complicated partial BR after conventional BCT presents a greater challenge for the surgeon than well-planned, immediate postmastectomy BR.^{32,55-57}

Nowadays beyond the oncological reasons, the patients as well as the surgeons opt for mastectomy more easily, even in cases of unfavourable location of the tumor, breast-to-tumor volume ratio or genetic disorders.

An increasing rate of IBR can be noticed nationwide in last two decades. The fact that IBR performed during therapeutic or prophylactic postmastectomy (in cases of appropriate patient selection) has become an oncologically accepted procedure providing excellent aesthetic outcome and quality of life, avoiding the feared cosmetic drawbacks of mastectomy.⁵⁸⁻⁶⁰ In the US, the percentage of mastectomies combined with IBR increased from 12.9% in 2000 to 36.3% in 2009, demonstrating the significance of IBR.⁶¹

IBR is performed at the same time as mastectomy. With the advent of SSM and its modifications such as areola-sparing mastectomy (ASM) and nipple-sparing mastectomy (NSM), the breast skin envelope can be partially or completely preserved. This in turn helps preserve the inframammary fold (IMF), which is an important aesthetic character of the breast, thus contributing greatly to the increased application of this surgical technique.^{36,62-64}

As outlined in the Guidelines of the National Comprehensive Cancer Network 2017 (NCCN) (version 1.2017) ⁶⁵, SSM is a safe procedure that provides improved cosmetic outcomes with adequate local cancer control; however, the guidelines emphasize appropriate patient selection and state the necessity of further prospective studies. Recent studies are mostly retrospective, indicate that the risk of LR is not increased in patients receiving SSM compared with that of those undergoing non-skin-sparing procedures. ^{63,64,66}

IBR encompasses several reconstructive plastic surgery techniques that can be safely performed in breast surgery centres under appropriate technical and personal conditions. It has become the most important tool of rehabilitation due to the immediate reconstruction of the form and volume of the breast. ^{18,27,60,67-69} Notably, the oncological safety of IBR has been verified by long-term follow-up data and meta-analysis of tens of thousands of cases collected over the past decades. ^{8,18,63,70-93} IBR does not influence the biology or prognosis of the tumor and does not hinder local control or physical/imaging examination. Although the complication rate of mastectomy with IBR is generally higher than that of standard mastectomy (SM), several studies indicate that the delay in adjuvant treatment is generally measured in days, not significant or significant, but does not have clinical relevance. Additionally it can be said that due to the retrospective nature of recent studies, high-quality evidence remains lacking regarding the oncological safety of IBR. ^{18,78,79,94}

The recommendation (2009) of the National Institute for Health and Clinical Excellence (NICE) includes the following: “The clinician has to discuss the opportunity of IBR with every single patient waiting for mastectomy when the co-morbidities or the adjuvant therapy do not mean contraindication. It is necessary to offer and describe in detail every alternative to BR, regardless of what is locally available.” The European Society of Breast Cancer Specialists subsequently proclaimed the fundamental rights of patients waiting for mastectomy on BR. ⁹⁵

1.4.1. Techniques of immediate breast reconstruction

IBR can be performed with silicone or saline-filled implants and/or tissue expander, autologous tissue or the combination of these. ^{18,36}

Nowadays the implant-based BR is the most frequent technique following mastectomy in breast cancer and/or BRCA 1/2 mutation carriers. ⁹⁶

The basic indication of IBR is early stage breast cancer; however the locally advanced breast

cancer and patients following neoadjuvant chemotherapy do not mean the absolute contraindication of IBR.^{18,65} The gold standard of care is the two-stage BR using a tissue expander. **(Figure 3.)** Based on the publication of Kronowitz et al. and according to the Guidelines of NCCN 2017 (version 1.2017), delayed BR (DBR) or so-called D-IBR is preferable in cases of planned or expectable RT, in which a remote valve tissue expander is placed under the subpectoral-subserratus position at the same time as the removal of the primary tumor^{18,65,97,98} **(Figure 4.)**

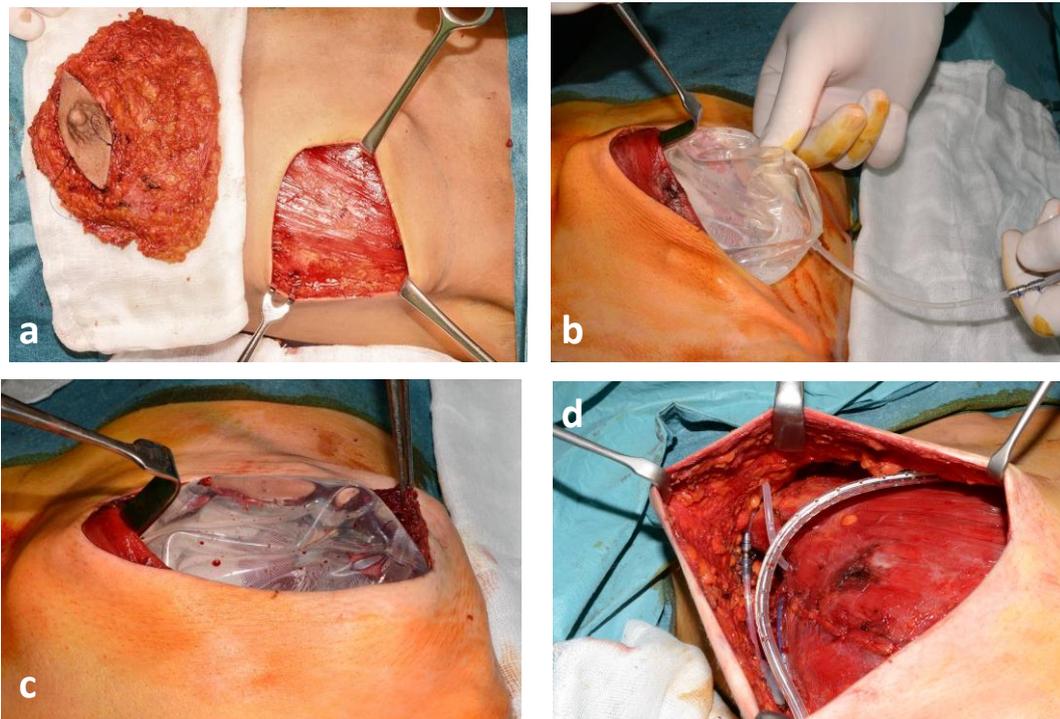


Figure 3. Pictures illustrating the technique of D-IBR. Following a right-sided skin-sparing mastectomy (a), a remote valve tissue expander was placed under the elevated musculi pectoralis major and musculi serratus anterior (b-c), then the edges of the elevated muscles were sutured to each other over the tissue expander (d)

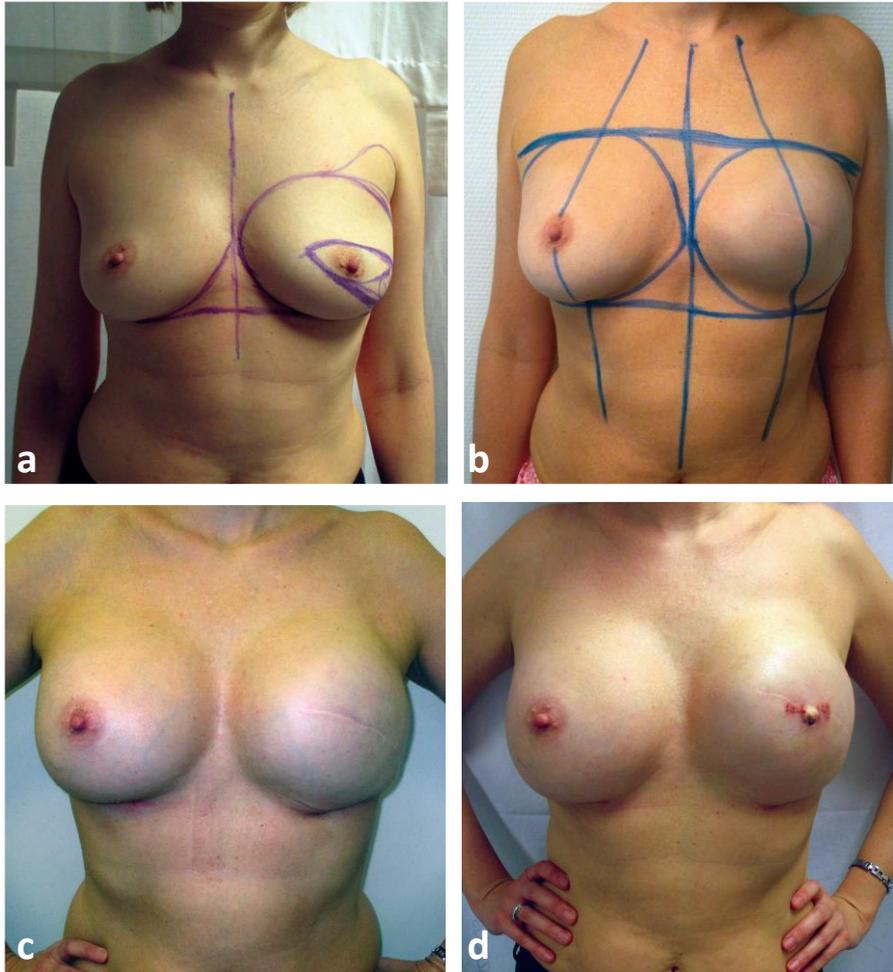


Figure 4. Pictures illustrating a left-sided delayed-immediate postmastectomy BR due to a *pT2pN0(sn)M0 ductal invasive carcinoma (ER: 90%, PR: 90%, HER-2: neg.)* (a) (b) a tissue expander placed in the subpectoral-subserratus position (c) an expander implant change with contralateral symmetrization and augmentation of the right sided breast at the 6th postoperative month (d) nipple reconstruction performed on the left side at the 9th postoperative month

D-IBR accounts for approximately 70% of all reconstructions according to statistics from the American Society of Plastic Surgeons.⁹⁶ However, single-stage direct-to-implant (DTI) BR has also become an accepted approach over the past decade.

1.4.2. Direct-to-implant breast reconstruction

DTI BR offers a biomechanically stable implant position with significant advantages. The second operation, with its related risks and morbidity, can be avoided. DTI BR decreases the time for convalescence, providing earlier restoration of body image and reduces costs.⁹⁹

In addition to the different types of SSMs, the so-called biological matrices (acellular dermal matrices [ADMs]) and other synthetic meshes play key roles in the popularity of DTI IBR.

In DTI IBR, an ADM patch covers the lower pole of the implant. The superior rim of the matrix holds (pulls and retains) the contracted and cranially shortened pectoralis major muscle. The lower rim of the mesh is fixed to the IMF. The pectoralis major muscle and the ADM patch not only create a complete pocket for the implant but also hold and support the lower pole of the reconstructed breast. The natural shape and form of the implant fills the lower pole of the breast without distortion or dislocation. Despite the advantages of ADMs, the related cost of the biological matrices is significant in health care systems.¹⁰⁰⁻¹⁰²

Due to their high cost, non-biological materials have been recently introduced including the polyglactin 910 (Vicryl[®]) mesh, TiLOOP[®] Bra, ULTRAPRO[®]-mesh, SERAGYN[®] BR mesh and the TIGR[®] Matrix as low-cost alternatives to ADMs. These non-biological materials may be able to satisfy the increased demand for DTI IBR, especially in developing countries.¹⁰³

In recent years, modern modalities of breast surgery, such as the OPS and IBR techniques, have become increasingly common in Western Europe and the US; however, their use has increased slowly in Hungary. Surgeons are gaining experience with these procedures. These techniques are very complex, requiring special plastic surgical knowledge and individualized surgical decision making to achieve good cosmetic results. However, according to the current literature, the decision of a breast surgeon regarding the optimal breast surgical method, e.g., based on the maximal tolerable volume loss of a given sized breast, is subjectively based on experience and there are few objective indicators supporting the decision making between BCS, OPS or mastectomy with IBR.

2. AIMS

1. Assess the aesthetic and functional outcomes and quality of life following breast-conserving therapy
2. Determine an objective algorithm in decision making between conventional and oncoplastic breast-conserving surgery or mastectomy with immediate breast reconstruction regarding the maximal tolerable volume loss of the breast
3. Assess the Hungarian data of the clinicopathological and aesthetic outcomes of immediate postmastectomy breast reconstruction
4. Provide the first assessment of the clinicopathological and aesthetic outcomes and quality of life with the use of ULTRAPRO[®] mesh as a low-cost alternative to biological matrices in single-stage direct-to-implant immediate postmastectomy breast reconstruction

3. Patients and methods

3.1. The aesthetic and functional prospective cohort study in decision making between conventional and oncoplastic breast-conserving surgery or mastectomy with immediate breast reconstruction

This prospective cohort study (ClinicalTrials.gov, Identifier: NCT01496001) was performed - approved by the institutional research ethics committee - between December 2011 and December 2013 at the National Institute of Oncology (NIO) and involved 350 female patients with early-stage, solitary, unilateral ($T \leq 30$ mm) breast cancer. The exclusion criteria were as follows: pregnancy, age older than 70 years, a history of breast or axillary surgery, centrally localized tumors, indications for mastectomy due to clinical status, subjective or objective breast asymmetry prior to surgery, more than 5% body weight loss or gain in the 12 months after the surgery, histological results requiring completion of the surgery or histological results not indicating RT.

Surgical technique and adjuvant RT

Each patient underwent a wide local excision (with an aimed macroscopical margin of 10 mms) and SLNB. All of the analyzed cases underwent WBRT, with an overall dose of 50 Gy and external beam, 6-MV photon irradiation, and, in 63 cases, the administration of an additional 16 Gy of tumor bed boost irradiation.

Assessment methods

Subjective aesthetic and functional factors were recorded using the internationally validated Breast Cancer Treatment Outcome Scale (BCTOS), which includes 22 items. Patients were instructed to rate each item on the BCTOS questionnaire on a four-point scale to evaluate the differences between the treated and untreated breasts.¹⁰⁴ The value of the score on each scale is the mean of the ratings for all of the items belonging to that scale.¹⁰⁵ A higher score reflects a poorer status (i.e., a greater difference between the treated and untreated breasts). If the subjective aesthetic and functional results rated by the patients had average scores of 2 or more, the results were considered unacceptable.

The EORTC Quality of Life Questionnaire was validated in Hungarian and used to measure the quality of life of breast cancer patients. Selected scales were used in the QLQ-C30 questionnaire, including social functioning, which consisted of 2 items, and emotional

functioning, which consisted of 4 items. The scale for body image from the QLQ-BR23 questionnaire also consisted of 4 items. Potential scores range from 0 to 100, with a higher score indicating a higher prevalence. For example, a higher score for emotional functioning predicts a better quality of life, whereas a higher score for a symptom-related scale represents a higher level of symptomatology.¹⁰⁶ The functional factors with scores of 50 or less and the symptomatic scales with scores of 50 or more were considered to indicate an unacceptable quality of life.

To exclude subjectivity, the aesthetic results were classified objectively based on photo documentation using the Breast Cancer Conservative Treatment-cosmetic results (BCCT.core) software (version 20).¹⁰⁷ BCCT.core software provides an extensive set of automated measurements using digital marks to establish a 4-point classification scale (excellent, good, fair and poor) and the overall assessment of cosmetic outcomes (**Figure 5**).^{108,109}

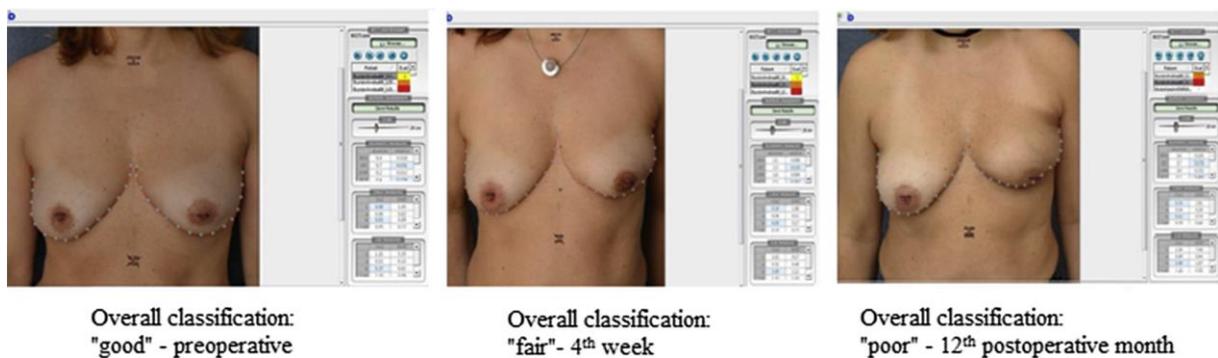


Figure 5. Examples of the classification of photographic images at 3 different times using BCCT.core software.

Digital frontal photographs of the breasts were obtained from all of the patients in a standardized manner - i.e., their arms at their sides and the suprasternal notch is included,- by a single photographer using a Nikon D3200, 24.2 megapixel digital camera. Objective aesthetic results classified as fair or poor by the BCCT.core software were considered unacceptable.

MRI (magnetic resonance imaging) of the breast was performed to document the oncological status and to calculate the contralateral breast volume. The breast MRI-volume calculations were performed at the GE AW 4.6 workstation, using the T1 FS or STIR sequences of the images. The non-representative parts of the measured breast were manually

excised and, following the setting of the threshold limit, the parts not forming the breast were removed from the remaining pixels. At the end of the process, the real volume of the breast was automatically calculated using the previously cited workstation's volume option. Then, the contralateral, non-tumorous breast volume was determined, to which the removed specimen volume from the tumorous breast was compared, thereby calculating the percentage of breast volume excised for each quadrant.

A limitation of this study was that only a single MRI scan was obtained at the time of the oncological staging, which was performed at the 12th postoperative month. The volume of the contralateral, non-malignant breast was assessed at that time. Therefore, the exclusion criteria were a preoperative objective aesthetic classification not scaled as excellent (i.e., >10% asymmetry between the breasts) based on the preoperative photos by BCCT.core, any asymmetry subjectively observed as evaluated by a committee of 3 breast surgeons, and a >5% weight loss or gain occurring between the preoperative and postoperative 12-month time period prior to the MRI volume assessment.

The excised specimen weights and 3-dimensional diameters were measured.

Assessment time points

Following BCS, the excised specimen weights and 3-dimensional diameters were measured.

The subjective aesthetic and functional factors, quality of life and objective aesthetic factors were recorded at three different times: preoperatively, at the 4th postoperative week following the BCS and at the 12th postoperative month following the adjuvant RT.

MRI was performed at the 12th postoperative month.

Statistical methods

A descriptive statistical analysis was performed to determine the mean and median values of the patients' ages, breast volumes, and percentages of breast volume excised.

The current literature indicates that breast density ranges from 0.8-1.2 g/cm³.^{110,111} According to the study of Parmar et al., no significant difference exists between the volume and the weight of the excised specimens. They observed the breast density to be 1.07 and 1.06 g/cm³.¹¹² For the specimen weight measurements in the present study, the mean breast density value of 1 g/cm³ was used. To evaluate the excised percentage of the breast volume in each case, the specimen weight was used for comparison to the non-malignant breast volume

measured by MRI at the 12th postoperative month; thusly, the percentage of breast volume excised for each quadrant was calculated. According to the NSABP-06 trial, the specimen shape after a wide excision is considered a sphere.^{6,113} Utilizing the same formula ($V = \frac{4}{3}\pi r^3$) used by Cochrane et al. in 2003,³² the specimen volumes (cm³) were calculated. The correlation between the weight of the specimens and the volume of the specimens was analyzed using Spearman's rank order correlation test using the mean breast density value (1 g/cm³).

According to the results from the 4th postoperative week regarding the effects of conventional BCS, the correlations between the percentage of breast volume removed and quality of life, subjective aesthetic and functional factors and objective aesthetic factors were examined using a Spearman's Rho statistical analysis.

The correlations between the percentage of breast volume excised and the specimen weight, as well as the clinical tumor size, were verified using a Kruskal-Wallis statistical analysis. Using receiver operating characteristic (ROC) curves, the maximal percentage of removable volume of each breast subregion was determined to obtain the maximal sensitivities and specificities regarding quality of life, subjective and functional results, and objective aesthetic results.

From the 4th postoperative week until the 12th month after BCS, the impact of the adjuvant RT on quality of life, subjective aesthetic and functional results, and objective aesthetic results were assessed using Friedman's ANOVA. Patient homogeneity was analyzed using a Mann-Whitney test by dividing the patients into two subgroups: the boost (n=63) and no boost (n=137) groups. To determine the median (min-max) values of the subjective aesthetic/functional factors, objective aesthetic factors, and quality of life (emotional functioning, social functioning, body image) in the 200 patients, the Wilcoxon signed-rank test was used.

3.2. The study of evaluation of the clinicopathological findings and cosmetic outcomes of 100 immediate, postmastectomy breast reconstruction cases

Therapeutic and partly contralateral, prophylactic, immediate, postmastectomy BR was performed on a total of 127 patients at the NIO from May 2011 to September 2014. 27 patients were excluded from the retrospective processing, the oncologic follow-up of 19 patients was performed in another institute, while 8 patients did not want to participate in the evaluation of the cosmetic result through personal or telephone inquiries.

A retrospective, clinico-pathological analysis was performed - approved by the institutional research ethics committee - on a prospective database, involving the remaining 100 breast cancer cases treated with immediate, postmastectomy BR.

The database included the patient's age, the location site of the tumor, the fact of genetic examinations and their results, the body mass index (BMI) of the patient, the clinical TNM, the time of the surgery, the type of the surgery, detailed information about the technique of the oncologic surgery (concerning the primer tumor and the regional lymph nodes) and the reconstructive surgery, the therapeutic or the prophylactic nature of the surgery, the duration of the surgery, the volume and the type of the applied implant (tissue expander, silicone implant).

The database included the histological type of the tumor, hormone receptor status, HER-2 status, grade, Ki67 value, pathological TNM, molecular subtype and the nature of the microscopic surgical margin. Additionally, it included the postoperative complication if it occurred, the initiation of the adjuvant treatment in relation to the time of surgery, the types of adjuvant multidisciplinary treatments (chemotherapy and/or targeted biological treatment and/or endocrine and/or RT), the time of follow-up from the time of surgery in months, and the oncologic status of the patient (tumor free, local or distant recurrence).

The final aesthetic outcome of the patients were assessed with personal or telephone self-assessment survey on a scale of 1-5 after the completion of the adjuvant treatments. Response to the survey was voluntary.

The diagnostics of breast cancer was performed in accordance with the rules of the profession in every case with complex imaging examination, additional MRI if necessary, histologic or cytologic confirmation. For regional staging ultrasound (UH) and the UH-guided needle aspiration cytology were used. According to institutional protocol in case of

appropriate indication chest X-ray, abdominal UH, bone-scintigraphy, computer tomography [CT]/MRI examination was performed for the exclusion of distant metastases (DM).

Surgeries were performed uniformly according to the institutional oncology protocol, based on the decision of the Multidisciplinary Oncology Committee. The examination did not influence the applied diagnostics and interventions, or the complex oncological treatment. Single-shot antibiotics (Cefazolin 2 g, iv.) and low molecular weight heparin (LMWH) – prophylaxis were used during every surgery.

At the time of the study a minimum of 1 mm tumor-free resection margin were considered as microscopically intact surgical margin.

Local inflammatory signs (redness, fever, warm to touch), hemorrhage (haematoma, suffusion), partial or total skin or nipple necrosis, fat necrosis requiring the revision or puncture of the wound, abnormal capsule formation around the implant, technical problems of the implants (deflation of the tissue expanders, rupture of silicone implants) and seroma lasting for more than 2 weeks observed during the 30 postoperative days were considered as complication.

The follow-up was performed according to the institutional protocol in every patients, thus physical examination was performed in every three months for the first two years, then in every six months until the fifth year. In case of early stage lymph node negative cases annual breast-UH and breast-MRI was performed, and mammography was performed in case of existing contralateral parenchyma, while chest X-ray and abdominal UH were parts of the follow-up in lymph node positive cases until the institutional protocol change in 2013, but after this modernization of the protocol we only performed these methods in case of complaints. The follow-up protocol was supplemented with chest-, abdominal- or pelvic CT and bone scintigraphy in case of advanced stages and - according to the renewed institutional protocol – complaints.

The data were analysed with descriptive and comparative statistical methods (Microsoft Excel 2013; χ^2 -test [age, duration of the surgery], size of the silicone implant/expander, cosmetic self-assessment, RT and cosmetic values, complications). Statistical significance was confirmed when p values were <0.05 .

3.3. The retrospective cohort study of the clinical experiences with the use of ULTRAPRO® mesh in single-stage, immediate, postmastectomy breast reconstruction in 102 patients

A single-institute, retrospective cohort study was performed - approved by the institutional research ethics committee - between January 2013 and January 2016 on a prospective database at the NIO. The study involved 112 early-stage breast cancer and/or BRCA 1/2 mutation carriers and evaluated 189 IBRs.

Patients underwent SSM, ASM or NSM followed by single-stage DTI BR using a partially absorbable lightweight ULTRAPRO® mesh.

All patients had textured, anatomical or round-shaped Mentor®¹¹⁴ silicone breast implants placed partially under the pectoralis major muscle, providing 40-60% coverage of the implants, while the lower pole was covered using ULTRAPRO® mesh (with an average size of 15x15 cm) for fixation and to maintain the unit of the infra- and lateral mammary folds. All surgeries were performed by three breast surgeons.

By 24 hours before the operation, informed verbal and written consent was provided by all patients regarding the exact surgical technique and ULTRAPRO® mesh, including its advantages and potential complications. All patients had an opportunity to choose other alternative techniques, such as D-IBR with tissue expander, immediate autologous (if the patient was an ideal candidate for this type of operation) or DBR. The type of surgery was chosen individually considering the patient's characteristics, oncological status, anamnesis, co-morbidities and expectations so that the study did not influence the decision prior to the surgery. According to the institutional protocol, follow-up occurred daily for the first 3-4 days, then once or twice weekly for the first 4 weeks and every 3rd month thereafter.

The data, including the patient's age, BMI, smoking habits, diabetic co-morbidity, cup size, oncological characteristics, history of BCT (pre-existing scars on the breast with previous RT), histological findings, follow-up time, time of surgery, type of conservative mastectomy, type of incision, shape and size of the implants and any postoperative complications, were reviewed in a retrospective fashion.

Postoperative complications were divided into two categories. Minor complications included grade I and II capsular contracture, seroma, infection treated with antibiotics, partial skin/ NAC necrosis that healed spontaneously and rippling. Complications requiring surgical intervention were classified as major complications included grade III and IV capsular contracture, haematoma, chronic seroma, relapse of IMF/implant malposition, partial skin/NAC necrosis and infection causing implant extrusion. To evaluate capsular contracture, a 4-point Baker classification ¹¹⁵ scale was used.

To record the palpability of implant borders and the smooth touch of the breast, a 5-point Likert scale ^{116,117} (score: 1, strongly disagree; 2, disagree; 3, undecided; 4, agree; 5, strongly agree) was used to judge the statement, “this case has no signs at all of palpable implant borders resulting in a smooth touch of the breast”.

To assess the aesthetic results, a 5-point Likert scale was also used to judge the statement, “this case has an excellent aesthetic outcome”. In the 3rd postoperative month, an evaluation was performed by a committee of 4 breast surgeons, who gave a single score for each case.

In the 3rd postoperative month, patients were instructed to rate each selected item on the internationally validated Hungarian version of the EORTC Quality of Life Questionnaire to measure their quality of life. Selected scales of the QLQ-C30 questionnaire were used and included social functioning, which consisted of 2 items, and emotional functioning, which consisted of 4 items. The scale for body image applied by the QLQ-BR23 questionnaire also consisted of 4 items. The scores ranged from 0 to 100, with a higher score indicating higher quality of life. ¹⁰⁶

To determine the mean and median values of the recorded factors, a descriptive statistical analysis and the Wilcoxon signed-rank test were used. Correlations between active smoking, diabetic co-morbidity, BMI, cup size C or D, previous RT with pre-existing scars, type of incision and the occurrence of minor as well as major complications were statistically analysed using Pearson’s chi-square or Fisher’s exact test. Relative risk was also determined to analyse the ratio of the risk of complications among patients exposed to a potential risk factor to those not exposed. A multiple regression analysis was applied to examine the association between the potential

risk factors and the observed complications. The statistical unit of analysis was the breast surgery cases. Statistical significance was confirmed when P values were <0.05 . All statistical analyses were performed using Statistica 12.0 (StatSoft, Tulsa, OK) or PAST 1.86.^{118,119}

Surgical technique of the DTI BR using ULTRAPRO[®] mesh (Figure 6. a-g)

The patient was marked preoperatively and positioned with the arms angled at approximately 70 degrees on the operating table. A single dose of antibiotic (cefazolin or ciprofloxacin) was administered 10-15 minutes before surgery. In every case of NSM or ASM, an incision was made partially at the IMF and partially at the lateral mammary fold between the 3 and 6 o'clock positions. In every case of SSM, a short horizontal incision was made centrally between the 3 and 9 o'clock positions.

After the ASM (which was the most commonly used technique), the next step was the creation of a partial subpectoral pocket for the implant with elevation of the pectoralis major muscle from the lateral to the medial direction. The origin of the muscle was slightly divided from the chest wall to approximately the 4 or 8 o'clock position to reduce its rigidity. Once the muscle was released, a 15x15 cm piece of ULTRAPRO[®] mesh was sewn to the lateral edge of the pectoralis major muscle with 2.0 Polysorb absorbable horizontal mattress sutures. Straining the ULTRAPRO[®] mesh makes it more flexible if the direction of the pulling is sheered to the blue lines of the mesh. If the direction of the pulling is parallel to the blue lines, the mesh is more rigid. While it is being sewn, the more flexible direction of the ULTRAPRO[®] mesh should be parallel to the lateral edge of the pectoralis major muscle. Afterward, a sizer was used to confirm proper pocket placement.

Finally, the selected implant was placed into the preformed pocket. The inferior and lateral parts of the ULTRAPRO[®] mesh were sewn to the chest wall and/or to the serratus anterior muscle using simple interrupted 2.0 Polysorb absorbable sutures, thereby maintaining the gentle curve and unit of the infra- and lateral mammary folds.

Prior to closure of the wound, a 16 Ch suction drain was placed along the IMF.

The mastectomy incision was then closed in two layers with continuous 3.0 Polysorb absorbable and 3.0 Surgipro non-absorbable sutures. The site of the removed mamilla was also sutured in two layers using tobacco-pouch 3.0 Polysorb absorbable and simple interrupted 4.0 Prolene non-absorbable sutures.

The wound was then coated with Betadine® gel and covered with semipermeable Mepore® dressing. The implants were stabilized with compression surgical bra use until the 6th postoperative week. Patients left the hospital usually on the third postoperative day, and the drains were removed if the output was less than 50 mL for a 24-hour period of time.

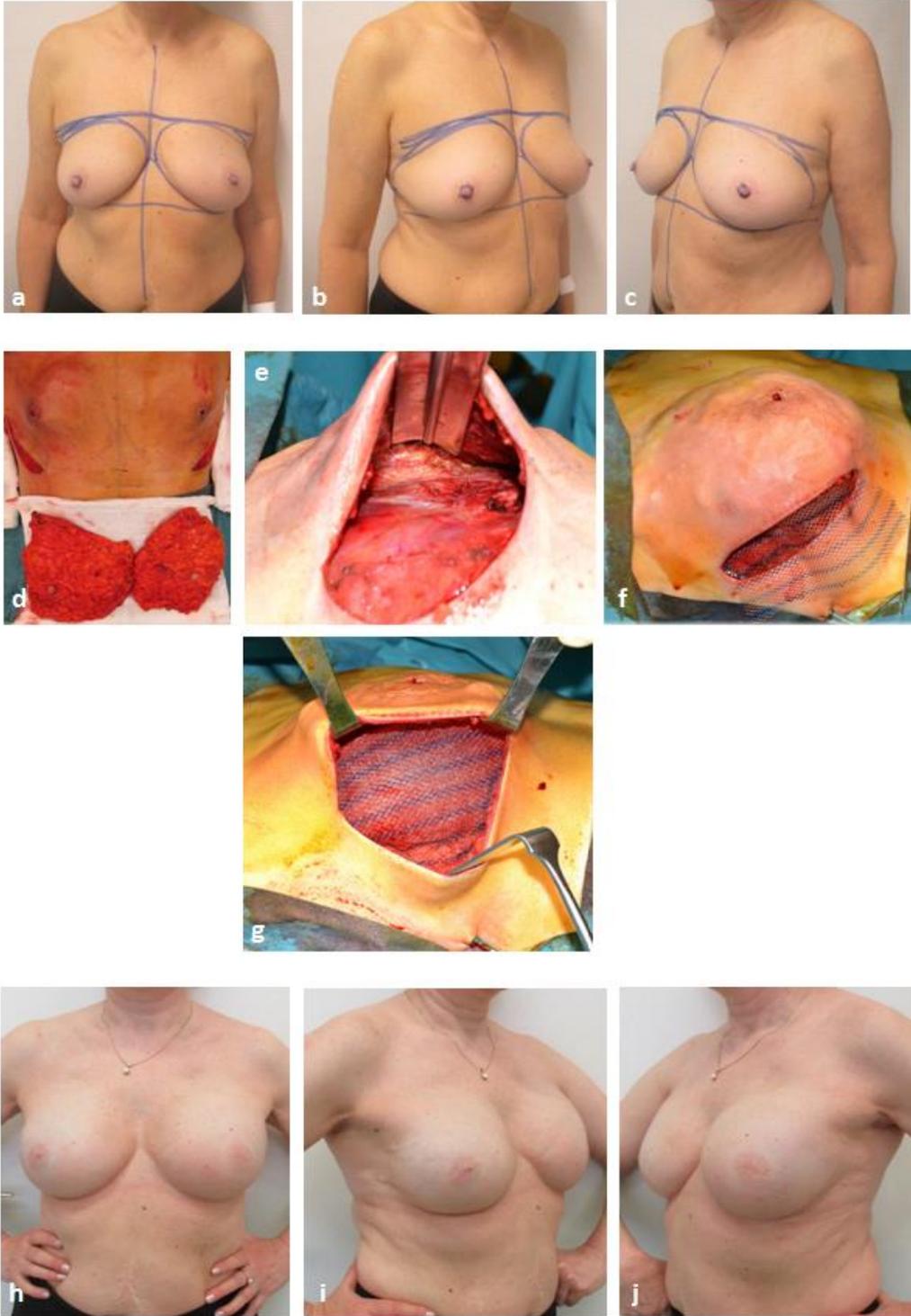


Figure 6. a-g. *Illustrating the surgical technique of IBR with the use of ULTRAPRO® mesh*
6. a-c. *Preoperative photo of a 49-year-old BRCA 2 carrier patient with a history of BCT on the left side.*

6. d. *A bilateral risk-reducing, ASM was performed with bilateral SLNB.*

6. e. *Elevating the pectoralis major muscle from the chest wall.*

6. f. *A 15x15 cm piece of ULTRAPRO® mesh was sewn to the lateral edge of the pectoralis major muscle with 2.0 Polysorb absorbable horizontal mattress sutures.*

6. g. *Anatomically shaped implants (545 cc) were placed into the preformed pocket on both sides. The inferior and lateral part of the ULTRAPRO® mesh was then anchored to the chest wall and to the serratus anterior muscle using simple interrupted 2.0 Polysorb absorbable sutures.*

6. h-j. *Pictures were taken at the 3rd postoperative month.*

4. Results

4.1. The aesthetic and functional prospective cohort study in decision making between conventional and oncoplastic breast-conserving surgery or mastectomy with immediate breast reconstruction

In total, 350 patients were enrolled in this study. One hundred fifty patients were excluded due to histological requirements for re-excision, mastectomy and/or ALND (n=61), histological results not indicating RT (n=15), more than 5% body weight loss or gain (n=67), or voluntarily patient withdrawal (n=7). After the homogenization of the investigated population, the remaining 200 patients were statistically analyzed. The average age was 56 years (range: 32-70, median=58, r=8.068), and the mean breast volume was 625.22 cm³ (range: 180-1950, median=550, r=305.656). The average percentage of breast volume excised was 14.73% (range: 2.72-40.81, median=13.20, r=7.27), and the average weight of the excised specimens was 85.58 g (range: 20-290, median=75.000, r=52.320).

Regarding the breast cancer staging characteristics of the patients, 15 women were pTisN0(sn), 132 were pT1a-cpN0(sn), 44 were pT2pN0(sn), 3 were pT0-1pN1mi(sn), 5 were pT3pN0(sn), and 1 was pT2pN3c. The mean pathological tumor size was 15 mm (range: 2-57 mm).

Following BCS, all patients underwent WBRT, and 63 received additional boost irradiation. In total, 174 patients received adjuvant endocrine therapy, 33 patients underwent adjuvant chemotherapy (6 cycles of FAC or FEC), and 34 patients underwent adjuvant biological therapy. The effects of these therapies on quality of life and on aesthetic and functional factors were not further investigated.

According to the results from the 4th postoperative week on the effects of conventional BCS, an increase in the percentage of breast volume excised resulted in quality of life changes, such as significant deteriorations in social functioning ($r=0.649$, $p<0.0001$), emotional functioning ($r=0.623$, $p<0.0001$), body image ($r=0.771$, $p<0.0001$), and effects on subjective aesthetic and functional factors ($r=0.623$, $p<0.0001$) and objective aesthetic factors ($r=0.684$, $p=0.0001$) (**Figure 7.**).

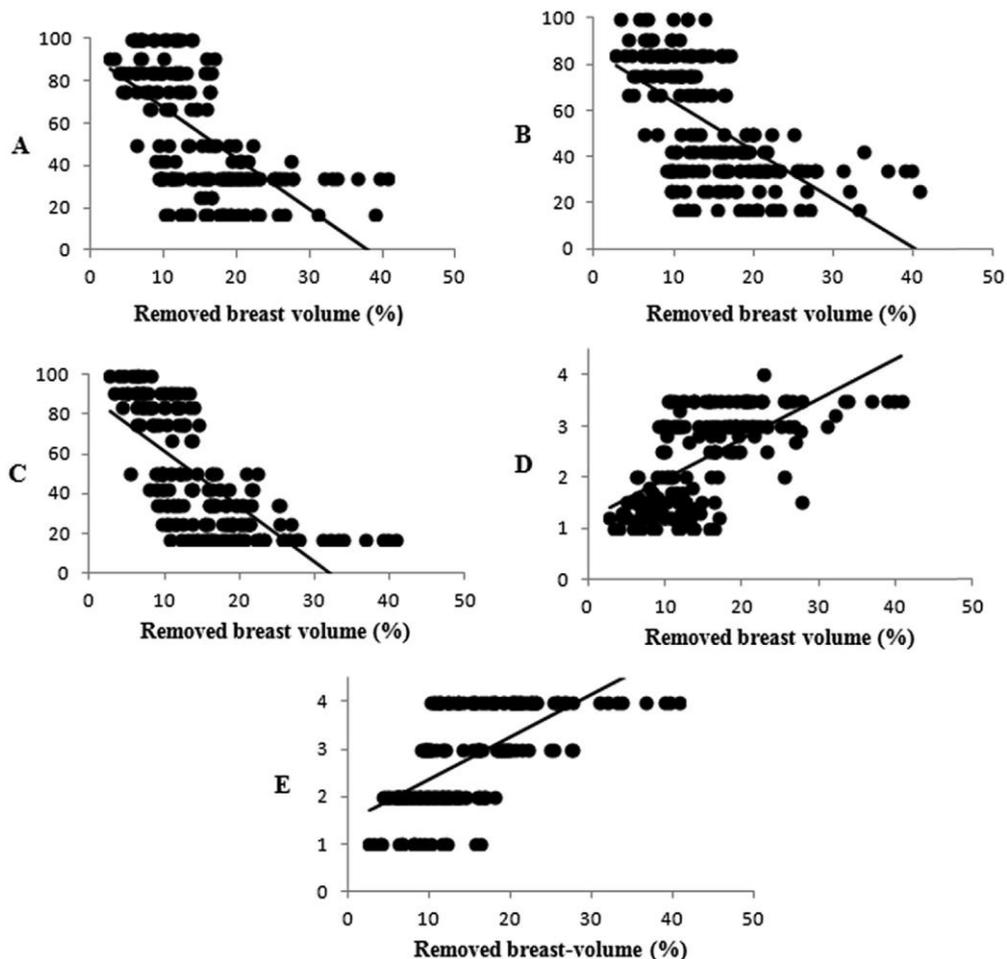


Figure 7. Significant deterioration was observed with an increase in the percentage of breast volume removed in relation to social functioning (A), emotional functioning (B), body image (C), subjective aesthetic and functional results (D), and objective aesthetic results (E).

A significant correlation was found between the weight and the volume of the excised specimens ($r=0.54$, $p=0.023$).

A significant correlation was found between the increase in specimen weight and the percentage of breast volume excised ($r=0.568$, $p<0.0001$). The same correlation was found between clinical tumor size and the percentage of breast volume excised ($r=0.400$, $p=0.0015$). With the clinical tumors divided into 5 subgroups according to their sizes, the average weight of the excised specimen was determined for each subgroup, as shown by the following data: 5-9.5 mm: 66.12 g, 10-14.5 mm: 73.60 g, 15-19.5 mm: 89.54 g, 20-24.5 mm: 95.00 g, and 25-30 mm: 137.65 g.

From the removal of the clinical tumors (sizes: 5-9.5 mm, 10-14.5 mm, 15-19.5 mm, and 20-24.5 mm), a trend was found between the clinical tumor size and the excised specimen weight. Tumors between 25 and 30 mm in diameter resulted in significantly greater specimen weight loss (137.65 g on average) than did smaller tumors ($p=0.0013$). Based on ROC curves, the maximal percentage of removable volume of each breast subregion was determined (**Table 3.**).

	Upper-outer quadrant (n=79)					Upper-inner quadrant (n=40)				
	Maximal cut-off value (%)	P	AUC	Sensitivity (%)	Specificity (%)	Maximal cut-off value (%)	p	AUC	Sensitivity (%)	Specificity (%)
Quality of life										
• <i>Emotional functioning</i>	18.26	<0.0001	0.992	97.37	97.56	9.48	<0.0001	0.983	88.24	95.65
• <i>Social functioning</i>	17.56	<0.0001	0.947	87.8	97.37	9.48	<0.0001	0.947	75	95
• <i>Body image</i>	18.85	<0.0001	0.959	80	97.73	8.88	<0.0001	0.973	87.5	95.83
Subjective aesthetic and functional results	18.76	<0.0001	0.955	97.40	97.20	8.88	<0.0001	0.983	100	88.24
Objective aesthetic results	18.26	<0.0001	0.955	97.56	97.37	8.88	<0.0001	1	100	88.24
	Lower-outer quadrant (n=40)					Lower-inner quadrant (n=41)				
	Maximal cut-off value (%)	P	AUC	Sensitivity (%)	Specificity (%)	Maximal cut-off value (%)	p	AUC	Sensitivity (%)	Specificity (%)
Quality of life										
• <i>Emotional functioning</i>	15.5	<0.0001	1	100	95.45	9.23	<0.0001	0.949	83.33	95.65
• <i>Social functioning</i>	16.07	<0.0001	0.998	100	95	9.53	<0.0001	0.943	80.95	95
• <i>Body image</i>	15.5	<0.0001	1	100	95.45	8.90	<0.0001	0.973	75	96
Subjective aesthetic and functional results	14.51	<0.0001	1	98	94.60	9.65	<0.0001	0.976	91.67	94.58
Objective aesthetic results	14.11	<0.0001	1	100	94.44	9.53	<0.0001	0.976	91.67	94.12

Table 3. The maximal percentage of volume that may be excised for each breast subregion. Statistical significance was confirmed when p values were <0.05 .

Table 4. shows the median values of patient satisfaction regarding the quality of life, the subjective aesthetic/functional results and the objective aesthetic outcome at the 4th postoperative week and at the 12th postoperative month following adjuvant RT.

	Postoperative 4 th week (n=200)			Postoperative 12 th month (n=200)			p
	Median	Min.	Max.	Median	Min.	Max.	
Quality of life							
• <i>Emotional functioning</i>	50.00	17.00	100.00	50.00	17.00	100.00	0.29
• <i>Social functioning</i>	67.00	17.00	100.00	67.00	17.00	100.00	0.56
• <i>Body image</i>	50.00	17.00	100.00	50.00	17.00	100.00	0.6
Subjective aesthetic and functional results	2.5	1	4	2.8	1	4	0.00013
Objective aesthetic results	2.4	1	4	2.7	1	4	0.00013

Table 4. *The median values of patient satisfaction regarding the quality of life, subjective aesthetic/functional results and objective aesthetic outcome at the 4th postoperative week and at the 12th postoperative month following adjuvant RT.*

Higher scores for quality of life (range: 0-100) predict better quality of life. Higher scores for subjective aesthetic/functional results and the objective aesthetic outcome (range: 1-4) reflect poorer status.

Regarding the boost (n=63) and no boost (n=137) groups, no significant difference was observed in the subjective aesthetic/functional results (p=0.11), objective results (p=0.19) or quality of life (emotional functioning [p=0.33], social functioning [p=0.42], body image [p=0.54]). This finding underscores the rationale for considering these two groups as one group (patients underwent adjuvant RT irrespective of receiving boost irradiation).

Assessing the impact of adjuvant RT from the 4th to the 12th postoperative month after BCS, a significant deterioration was found in the subjective aesthetic and functional factors ($p=0.00013$) and in the objective aesthetic parameters ($p=0.00013$), whereas a statistical correlation between quality of life and RT was not verified.

4.2. The study of evaluation of the clinicopathological findings and cosmetic outcome of 100 immediate, postmastectomy breast reconstruction cases

121 IBR postmastectomy IBRs were performed among the patients involved in the study. The average age of the patients was 42.6 years (range: 25-64 years) with a mean BMI of 23.2 (range: 18-38).

The genetic examination of BRCA1/2 gene was performed in 70 cases, of which 42 cases were negative, while BRCA1 gene mutation was confirmed in 18 cases and BRCA2 gene mutation was confirmed in 10 cases. 43 surgeries affected the left breast and 36 the right one, while in 21 cases bilateral IBR were performed. The tumor was solitaire in 87 cases and multi-center in 13 cases. The tumor was affected both of the breasts simultaneously in 7 cases. ALND was performed in 17% of the cases, while SLNB was performed in 83%, of which a second, so-called reSLNB was performed in 4 cases. SM was performed in 14%, SSM in 64%, ASM in 20% and NSM in 2%. **Table 5.** shows the characteristic data of the tumors.

pT		(n)
pTis		13
pT1mi		4
pT1b		1
pT1c		38
pT2		35
ypT0		1
ypT1a		1
ypT1c		3
ypT2		4
pN		(n)
pN0		67
pN1		21
ypN0		4
ypN1		7
ypN2a		1
ER		76
PR		68
HER2		13
DCIS		(n)
Low Grade		1
Intermediate Grade		3
High Grade		9
Grade		(n)
I.		15
II.		34
III.		38

Table 5. *Oncological characteristics of 100 breast cancer patients*

The ST of the tumor showed the following distribution: ST. 0: 13%, ST. IA: 36%, ST. IB. 3%, ST. IIA: 31%, ST. IIB: 16%, ST. IIIA: 1%. Molecular subtypes of invasive tumors (n=87) were the followings: luminal A 42 cases (48%), luminal B 19 cases (22%), luminal B HER-2 positive 6 cases (7%), non-luminal 2 cases (2%), triple negative 18 cases (21%). The surgical margin was microscopically negative in 98 cases and positive in 2 cases concerning the anterior margin. The tumor was located centrally in both cases, thus we completed the surgery with the excision of the skin along with the removal of the areola. IBR was performed with tissue expander placed in subpectoral-subscapular position in 70% of the cases.

In 14% of the cases IBR was performed with LD myocutaneous flap, 3% performed with LD and expander, 5% with the combination of LD + silicone implant, 5% with subpectoral silicone implant supplemented with the strengthening of the lower pole with partially absorbable ULTRAPRO® mesh and it was performed with the reconstruction of

TRAM flap in 3% of the cases. Autologous free flap IBR during the reference period was not performed.

The average duration of the surgery was 132 minutes (range: 60-370 minutes). The average size of the applied implant was 460 cm³ (range: 260-650 cm³), the filling volume of the expanders was 477 cm³ (range: 300-800 cm³).

Early postoperative complication was observed in 18 cases (14,8%): inflammation in 5 cases (4.1%) bleeding requiring reoperation in 4 cases (3.3%), skin necrosis in 4 cases (3.3%), seroma causing complaints after the removal of the drain thus requiring UH-guided puncture in 4 cases (3.3%), and fat necrosis in one case (0.8%). Implant/expander technical problem occurred in 3 cases (2.4%), thus it was necessary to replace the implant/expander, and the capsular contracture was of such extent in 1 case (0.8%) that the wound line sutured in layers opened on the fourth week after the expander-implant replacement procedure, and the silicone implant came into contact with the environment and contaminated with the pathogens of the skin.

The average time of the initiation of the adjuvant treatment was 4.8 weeks (range: 4-12 weeks). Adjuvant RT was performed in 32 cases, adjuvant chemotherapy ± targeted biological therapy was performed in 42 cases and endocrine therapy was performed in 75 cases.

The average duration of follow-up period was 29.4 months (range: 16-56 months). Every patient was alive at the last follow-up appointment. No diagnostically unassessable lesion remained during the control imaging examinations after the surgery. Locoregional recurrence – as an infraclavicular metastatic lymph node- appeared 4 months after the surgery in one patient, who had therapy resistant triple negative subtype of the tumor. DM during the follow-up period was not detected.

40% of the patients were highly satisfied with the cosmetic results, 49% were substantially, 9% moderately and 2% minimally.

The duration of the surgery showed significant correlation with the type of the oncologic surgery (NSM, ASM versus SSM, SM) ($p=0.049$) and the chosen reconstruction surgery (subpectoral/subserratus expander, subpectoral silicone implant + ULTRAPRO[®] mesh versus LD myocutaneous flap, LD + expander /silicone implant, TRAM flap) ($p=0.002$) with

comparative statistical analysis. Significant correlation between the duration of the surgery, the type and the complication could not be confirmed. The duration of the bilateral surgery was longer in BRCA-positive patients ($p=0.01$), but it did not lead to higher complication rate. Statistical correlation was not verified between the final cosmetic result and the age of the patients and the type of the chosen surgery (neither mastectomy nor reconstructive surgery) or the applied silicone implant/expander thus the volume of the breast. Adjuvant RT did not influence significantly the final cosmetic outcome, only a tendency ($p=0.10$) showed among them. However, there was a significant correlation ($p=0.006$) between the patients' BMI and the self-assessment of the aesthetic result, overweight patients were less satisfied with the cosmetic results of the reconstructed breast.

4.3. The retrospective cohort study of the clinical experiences with the use of ULTRAPRO[®] mesh in single-stage, immediate, postmastectomy breast reconstruction in 102 patients

Ten patients were lost to follow-up because they did not complete the EORTC questionnaire. As a result, a total of 102 patients underwent immediate DTI BR using ULTRAPRO[®] mesh, representing 174 breast surgery cases. The mean age of the patients was 43 years (range: 25-61 years). The average follow-up time was 23.4 months (range: 3-36 months). The mean BMI was 23.2 (range: 16.9-30.4). Forty-six patients had a history of BCT (45.1%), resulting in 46 DTI BR cases (26.4%) with pre-existing scars on the breast and previous RT. Patient cup size, smoking habits, history of diabetes, and BRCA status are summarized in **Table 6**.

Patient characteristics	n (%) / range
BRCA 1/2 +	76 (74.5%)
Active smoker	11 (6.3%)
Diabetic co-morbidity	8 (4.6%)
Cup size	
A	19 (18.6%)
B	46 (45.0%)
C	24 (23.5%)
D	13 (12.7%)

Table 6. *Patients' BRCA status, smoking habits, history of diabetes and cup size*

Seventy-two patients underwent bilateral DTI BR, and a unilateral procedure was performed in thirty cases. Among the operated breasts, 54 cases (31%) were oncologic, and 120 cases (69%) were for risk reduction. In cases of unilateral procedures, 4 patients were positive for BRCA 1/2 gene mutations, 19 patients had cTisN0, and 11 patients cT1a-cN0 breast cancer. Among the 72 bilateral DTI BR cases, all patients were positive for BRCA 1/2 gene mutations, and 22 patients had cTisN0 breast cancer in one breast. According to the final histological results, a total of 39 stage 0 and 15 stage IA breast cancer cases were verified.

ASM was performed in 68% of cases, while SSM and NSM were performed in 27% and 5% of the cases, respectively. The average operative time was 78 minutes per case (range: 58-110 minutes).

All implants were textured, silicone gel-filled devices, with the majority of them anatomically shaped (65% anatomical, 35% round-shaped). The mean size of the implants was 480 cc (range: 395-700 cc).

Complications included eight infections (4.5%), five of which (2.8%) resolved with antibiotic and anti-inflammatory treatment. The other three cases (1.7%) required revision and drainage without removal of the mesh or the implants. Haematoma occurred in two cases (1.2%). Both cases required surgical evacuation of the contents. Five (2.8%) of the total of nine seroma cases (5.1%) became chronic, requiring revision and drainage. Partial skin/NAC necrosis causing implant extrusion occurred in seven cases (4.0%). Four of these cases (2.3%) required necrectomy and subsequent autologous salvage using intercostal artery perforator flaps to fill the defects. Relapses of IMF and/or implant malposition were found in four cases (2.3%), which required capsuloplasty. Capsular contracture (Baker III/IV) was identified in two breasts (1.2%), indicating capsulectomies with implant removal and delayed reconstruction using LD myocutaneous flaps and tissue expanders in each case.

Overall, there were 12 minor complications (6.9%) and 20 major complications (11.4%) requiring surgical intervention, for a total of 32 complications (18.3%).

There were no significant correlations between active smoking ($p=0.211$), diabetic comorbidity ($p=1$), BMI ($p=0.126$), cup size C or D ($p=0.344$), type of incision ($p=0.292$) and

the development of complications. However, breast surgery cases with a history of BCT did have a significantly higher complication rate.

According to the contingency table, complications occurred in 50% of the breast surgery cases in which previous BCT was performed. Complications were observed in 7.8% of the breast surgery cases without a history of BCT. The variance between these two groups was statistically significant ($p < 0.00001$).

The relative risk of complications with previous RT and pre-existing scars on the breast was 7.11 (95% CI: 3.558, 14.222) indicating a seven-fold higher incidence of complications than in cases without these factors.

According to the results of the multiple regression analysis, a history of BCT was a significant predictor of the risk of developing a postoperative complication (**Table 7**).

	<i>Beta</i>	<i>Standard error of beta</i>	<i>P</i>
<i>Intercept</i>	-0.013401	0.078653	0.865
History of BCT - yes vs. no	0.448031	0.068468	<0.00001
Incision type (ASM vs. SSM vs. NSM)	0.022062	0.051544	0.669
BMI (<25 vs. >25)	0.056678	0.074309	0.447
Cup size (A or B vs. C or D)	0.056609	0.073724	0.444
Non-diabetes vs. diabetic co-morbidity	0.100989	0.138640	0.467
Non-smoker vs. active smoker	-0.017486	0.131792	0.895

Table 7. Multiple regression analysis showing associations between potential risk factors and the observed complications. Statistical significance was confirmed when p values were < 0.05 .

At the 3rd postoperative month, assessing the results of the EORTC questionnaire rated by the patients, the median value of emotional functioning was 91.67 (min-max: 50-100), whereas the median social functioning score was 83.4 (min-max: 50-100). The median score of body image was 83.4 (min-max: 33-100).

The majority of breast surgeons agreed with the statement that “this case has no signs at all of palpable implant borders resulting a smooth touch of the breast”, with a mean score

of 4.1. Most of the breast surgeons agreed with the statement that “this case has an excellent aesthetic outcome”, with an average score of 4.0.

5. Discussion

5.1. Assessing the aesthetic and functional outcomes and quality of life following breast conserving therapy - based on the results of study 4.1.

A major drawback of BCT is the occurrence of unfavorable cosmetic results, which has been found in up to 33% of patients.¹⁹⁻²² The volume of tissue excised is the most important factor relating to cosmetic outcome.^{120,121} Other factors influencing the final aesthetic results are the patient’s age^{122,123} BMI,¹²⁴ breast size,¹²⁵ tumor location,^{126,127} tumor size,¹²⁷ incision placement^{124,125,128,129}, type of conservation surgery (quadrantectomy or wide excision)¹³⁰, number of re-excisions¹²⁰, chemotherapy^{124,127} and irradiation.^{104,127}

Recent studies have suggested a high risk of significant defects when 20% of the breast volume is excised³⁰, whereas Stevenson et al. found that high risk correlated to the removal of >12% of the volume.³¹ Cochrane et al. concluded that cosmesis and patient satisfaction were adversely affected when the estimated percentage of breast volume excised was >5% for medial tumors and >15% for lateral tumors.³²

This prospective cohort study also shows that the percentage of breast volume excised was significantly correlated with cosmetic and functional outcomes and quality of life.

BCSes were performed approximately equally among 8 general surgery specialists, which resulted in variability. Therefore, the expected specimen weight loss for a given sized tumor was determined, clarifying that the clinical tumor size may be a predictive factor of the aesthetic outcome for a given sized breast.

In general, physicians have considered cosmesis as either excellent or good in 55% to 94% of patients following RT (with a median follow-up of ≥ 3 years).^{125,128,131,132}

In an older study by Harris et al.,¹⁰⁸ physicians rated the cosmetic results as good or excellent in 66% of patients following primary RT.

The current study also shows a significant deterioration in subjective and objective aesthetic results following RT. With conventional BCS, a relatively large residual open cavity may remain and may be filled with a hematoma or seroma, which notably worsen wound healing and may serve as a basis for adjuvant RT-enhanced fibrotic reactions.¹³³

With OPS techniques, no residual open cavity remains in the breast using different volume displacement and replacement techniques or may be with mastectomy and IBR, thereby avoiding the aforementioned complications.

Preoperative surgical planning should include the breast volume, tumor location and the expected volume loss, enabling each patient to receive an individual reconstruction, however there are few objective indicators without definite consensus in decision-making between conventional BCS, OPS or mastectomy with IBR, basically determined by the surgeon's experience.

5.2. Determining an objective algorithm in decision making between conventional and oncoplastic breast-conserving surgery or mastectomy with immediate breast reconstruction regarding the maximal tolerable volume loss of the breast - based on the results of study 4.1.

Studies on the point at which the aesthetic and functional results and the quality of life following conventional BCS are so poor that a woman might have been better served by OPS or mastectomy and reconstruction are relatively few and highly variable.

Our aim was to determine the upper limit of the percentage of breast volume that could be excised before conventional BCS could no longer offer adequate cosmetic and functional results and a satisfactory quality of life.

Based on our findings conventional BCS did not result in unacceptable aesthetic or functional results or in a decreased quality of life when the percentage of the volume removed reached but did not exceed 18-19% in the upper-outer quadrant, 14-15% in the lower-outer quadrant, 8-9% in the upper-inner quadrant, and 9-10% in the lower-inner quadrant.

In cases involving a predictably larger volume loss than discussed above and in patients with medium or large breasts, oncoplastic BCS might be a better treatment choice than conventional BCS, whereas patients with small breasts might benefit from mastectomy and reconstruction (**Figure 8.**)

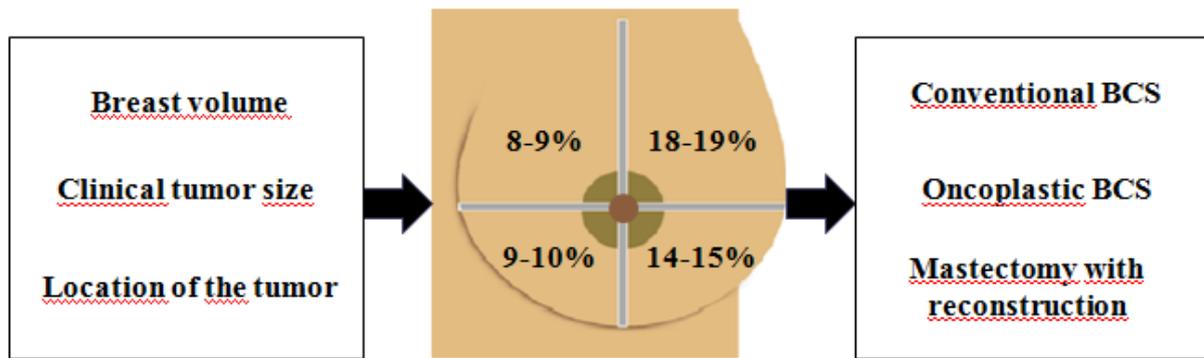


Figure 8. The algorithm used to determine the appropriate surgical strategy, considering the maximal breast volume loss

In current literature the approach of Clough et al is also known according to the anticipated resection of the breast. The volume displacement procedures were classified into two levels: (I) Including excision of less than 20% of breast volume, without neither skin excision nor mammoplasty; (II) Including anticipated resection of 20–50% breast volume, with excision of excess skin required to reshape the breast based on mammoplasty techniques. However, volume replacement procedures are still possible to use, in small or medium size breasts, even if only 20–50% of the breast volume is anticipated to be resected.^{23,41,134}

The limitation of this prospective study was that at the 12th postoperative month, for financial reasons, only a single MRI scan was performed at the time of the oncological staging, the point at which the non-malignant breast volume was assessed as the comparator for the excised specimen weight. From the 4th postoperative week to the 12th month after BCS, the impact of adjuvant chemotherapy and endocrine and biological therapies on the subjective aesthetic/functional factors and the quality of life were not further investigated.

A strength of the study was the 12-month prospective evaluation based on objective (photo documentation, internationally validated computer program) and subjective (internationally validated questionnaires) measurements. The calculated cut-off values for each breast quadrant contribute more objective information to the literature, which may aid the preoperative decision-making process.

5.3. Assessing the Hungarian data of the clinipathological and aesthetic outcomes of immediate postmastectomy breast reconstruction - based on the results of study 4.2.

In the past decade, there have been marked trends toward higher proportions of BCS-eligible patients undergoing mastectomy, bilateral prophylactic mastectomy with IBR. Among the factors that can explain this underutilization of BCS are patient and surgeon concern for LR, a family history of breast cancer or mutations in the BRCA genes or unpleasant cosmetic outcome especially in patients with unfavorable tumor-to breast volume ratio. ^{19-23,32,53-57}

With an advances of breast surgery i.e. IBR, the feared consequences of mastectomy could be avoided. Current IBR techniques are able to provide psychological, social, emotional, and functional improvements, including improved psychological health, self-esteem, sexuality, and body image without compromising the oncological outcome. ⁵⁸⁻⁶⁰

Three issues have arisen about the IBR: 1. Does reconstruction influence the biology and the prognosis of the tumor? 2. Do the special complications of the IBR affect adjuvant treatment? 3. Does it make the local control more difficult during physical and imaging examinations? ^{8,18} Based on the current scientific evidence it can be stated that the answer is no for all the three issues in case of applying multidisciplinary oncologic therapy in biological approach based on the better understanding of the molecular background of the tumor, and using the protocol of modern imaging techniques. ^{8,18,63,70-93} It is important to note that the oncological safety of IBR is verified by the long-term follow-up data and their meta-analysis from tens of thousands of cases collected over the past decades, but to this day the result of a prospective and randomized study in the comparison of the conventional and modified mastectomy (SSM, ASM, NSM) and the IBR is still not known. ¹⁸

The IBR did not change the oncologic results, the ratio of LR or the ratio of DMs significantly in clinical examinations (**Table 8.**) ⁸⁶⁻⁹³

Cohort study	Publication (year)	Stage (AJCC)	Follow-up (month)	Local recurrence (LR/AC)	Distant metastases (DM/AC)
Nedumpara et al. ⁸⁶	2011	I-IIB	55	IBR: 12/136 M: 38/691	IBR: 39/136 M: 89/691
Lim et al. ⁸⁷	2010	IIB-III	IBR 62,5 M: 50,6	IBR: 4/87 M: 20/810	IBR: nr M: nr
Gerber et al. ⁸⁸	2009	0-III	101	IBR: 12/108 MRM: 15/130	IBR: 12/108 MRM: 14/130
McCarthy et al. ⁸⁹	2008	I-III	68,4	IBR: 21/309 M: 25/309	IBR: 38/309 M: 49/309
Huang et al. ⁹⁰	2006	I-III	40	IBR: 3/82 MRM: 2/109	IBR: 10/82 MRM: 17/109
Murphy et al. ⁹¹	2003	0-IV	75,4	IBR: 2/158 M: 9/1262	IBR: nr M: nr
Vandeweyer et al. ⁹²	2001	0-IIB	72	IBR: 2/49 M: 1/49	IBR: 11/49 M: 10/49
Newman et al. ⁹³	1999	IIB-III	58,4	IBR: 5/50 MRM: 9/72	IBR: 16/50 MRM: 26/72

Table 8. *Oncological outcome (regarding local or systemic recurrence) of IBR compared with mastectomy without IBR*

AJCC: American Joint Committee on Cancer; M: mastectomy; MRM: modified radical mastectomy, nr.: DFS and OS are unknown; LR: local recurrence; DM: Distant metastases; AC: all cases

The prognosis of the oncology process – including LR – is principally determined by the biological properties of the tumor, the molecular subtype and the stage of the tumor, which must also be acknowledged in case of the evaluation of surgical treatment (for example: NSM is recommended especially in case of low-risk tumors).^{18,78,79} Neither the implant, nor the autologous tissue reconstructions do not influence the timely detectability of the recidives with modern imaging techniques (breast UH, MRI).^{8,83}

None of the control imaging examinations verified “diagnostically uncertain lesion” or “unassessable lesion” in the current retrospective study.

The complication rate of mastectomy with IBR is generally higher than the complication rate of SM, but according to several studies the “retardation” of adjuvant treatment is measured in days generally, not significant or significant, but does not cause the cancellation of the adjuvant therapy and basically does not have clinical relevance.^{78-80,82,94,135}

The IBR did not retard the initiation of the adjuvant treatment in the current retrospective analysis.

A complex decision-making process is required for IBR, as well as accurate preoperative examination, multidisciplinary oncology treatment plan, patient-related individual parameters (physique, BMI, size and form of the breast, scars, quality of the skin, smoking, comorbidities), possibilities of the surgical center, preparedness of the operating staff (for example microsurgery), and the will of the properly informed patient.¹⁸

DBR or so-called D-IBR is preferable in cases of planned or expectable RT, in which a remote valve tissue expander is placed under the subpectoral-subserratus position at the same time as the removal of the primary tumor.^{18,72,97,98} We achieved good results with the latter method - which was the most frequently used surgical procedure - in our practice. IBRs with tissue expanders placed into a submuscular position did not increase the complication rate and the surgical burden, and provided the possibility of a safe runoff of the adjuvant treatments by ensuring the correct breast shape, thus bridging the post-treatment period.

In general, the IBR requires a shorter hospital stay compared to DBR and it is more cost-efficient by reducing the number of the surgeries.⁸

According to the data of the 3rd National Mastectomy and Breast Reconstruction Audit in UK, complications appeared in 10% of the patients who underwent a mastectomy, while this ratio was 15-18% in the IBR-group depending on the technique of the reconstruction.¹³⁶ Mortality is negligible.

The early complication rate was 14.8% in our retrospective analysis, which complies with international results.

Only 10% of patients who underwent a mastectomy and 16.6% of patients who underwent an IBR required hospital readmission due to late complications.¹³⁶ Antibiotic therapy was required in 20% of mastectomy patients, while this ratio was 25% in the IBR-group. Multiple puncture of the seroma was required in 50% of the patients who underwent a

mastectomy ± IBR, while this ratio was just 30% in case of DBR, therefore, prolonged seroma formation is primarily connected to mastectomy, not to reconstruction in case of assessing the issue of delayed adjuvant treatment.¹³⁶

It should be noted that this study describes the medium-term results of IBR after mastectomy, a more accurate assessment of the oncologic safety requires further follow-up.

5.4. Providing the first assessment of the clinicopathological and aesthetic outcomes and quality of life with the use of ULTRAPRO® mesh as a low-cost alternative to biological matrices in single-stage direct-to-implant immediate postmastectomy breast reconstruction- based on the results of study 4.3.

The gold standard of care is two-stage BR using a tissue expander,⁹⁶ however, single-stage DTI BR has become an accepted approach over the past decade – accounting approximately 37 % of immediate reconstructions following mastectomy in the UK - offering a biomechanically stable implant position without second operation and its related risks and morbidity. DTI BR decreases the time for convalescence, providing earlier restoration of body image.⁹⁹

Beyond the certain types of SSMs, the so-called biological matrices have an important role in popularity of DTI IBR.

ADMs are used to maintaining the inferolateral unit of the breast covering partially the implant (or the tissue expander) at the time of IBR. Numerous benefits have been reported with their use including improved fold control, better support and control of the implant pocket with concomitant reduced risk of malposition, and improved lower pole expansion.

Recent studies have reported complication frequencies in DTI- and ADM-assisted BR ranging from 3.9%¹³⁷ to 69.5%¹³⁸ According to currently available reviews of biological materials such as ADMs, the infection rate ranges between 0.2 and 35.8%.^{137,139-161} Mastectomy skin flap necrosis or skin breakdown requiring operative revision has been reported in up to 9.1% of cases.¹⁴³ Minor skin flap necrosis or superficial epidermolysis responsive to conservative management was more frequent, reported in up to 28.7% of breasts.¹³⁸ The presence of seroma was found to range between 1.5%¹⁴³ and 24.3%¹⁵⁶. Haematoma formation after BR with ADM occurred in a smaller range of 0–11.1% of breasts.^{99,155,162-164}

The majority of studies reported few or no capsular contractures (six studies), with a range between 0.4 and 8.1%^{137,158} when ADM was used. Moyer et al.¹⁵⁵ studied the effect of radiation on ADM and capsule formation, revealing a very high rate of Baker class III/IV capsular contracture (33.3%). Thirty-nine studies evaluated explantation and implant loss in BR with ADM, with rates ranging from 0 to 33.3%.^{155,163,165,166}

Despite the advantages of ADMs, the related cost of the biological matrices is significant in health care systems.¹⁰⁰⁻¹⁰² The use of synthetic materials in BR is becoming more common as a low-cost alternative to ADMs.¹⁰³

The goal of this retrospective study of the use of ULTRAPRO[®] mesh in DTI BR was to evaluate a potential, less expensive alternative to biological matrices. In the current health care environment, cost is increasingly important, especially in developing countries. A 15 cm × 15 cm sheet of ULTRAPRO[®] mesh costs approximately €30, while a single sheet of ADM can range anywhere from \$1825 to \$4856, depending on its size and thickness.^{167,168}

The present retrospective cohort study showed that DTI BR using ULTRAPRO[®] mesh can provide good aesthetics (**Figure 6.h-j**), a satisfactory quality of life and acceptable emotional/social functioning and body image.

The overall complication rate was 18.3%, with a rate of surgical intervention of 11.4%. The most common complication was seroma formation (5.1%), while infection (4.5%) was found to be the second most common complication.

It should be noted that complications occurred in 50% of the breast surgery cases in which previous RT was performed with pre-existing scars on the breast. This rate was seven-fold higher than in cases without these factors.

The previous correlation was further validated by Spear et al.¹⁶⁹, Brooke et al.¹⁴⁰ and Pestana et al.¹⁷⁰, who reported a significant increase in overall complication rates when ADMs were used in irradiated patients.

As reported by recent studies, several different synthetic meshes are used in DTI BR as a low-cost alternative to ADMs. (**Table 9.**)

	Polyglactin 910 (Vicryl®) Mesh in DTI BR; Tessler et al. ¹⁷¹; 2014	Polyglactin 910 (Vicryl®) Mesh in DTI BR; Faulkner et al. ¹⁷²; 2014	TiLOOP® Bra in DTI BR, Dieterich et al. ¹⁷³; 2014	TIGR® Matrix Mesh in DTI BR, Schrenk ¹⁷⁴; 2016
No. of patients	50	155	207	29
No. of breast surgery cases	76	254	231	37
<u>Complications</u>	n (%)	n (%)	n (%)	n (%)
<i>Infection</i>	1 (1.3%)	4 (1.6%)	14 (6.1%)	0
<i>Haematoma</i>	0	0	22 (9.5%)	0
<i>Seroma</i>	0	0	11 (4.8%)	0
<i>Mastectomy flap/skin or NAC necrosis</i>	2 (2.6%)	0	18 (7.8%)	1 (2.7%)
<i>Implant/synthetic mesh explantation or implant exposure</i>	1 (1.3%)	12 (4.7%)	18 (7.8%)	1 (2.7%)
<i>Capsular contracture</i>	1 (1.3%)	9 (3.7%)	5 (2.2%)	0
<i>Ill-defined IMF</i>	n/a	n/a	n/a	n/a
<i>Minor complications (treated conservatively)</i>	2 (2.6%)	10 (4.0%)	36 (15.6%)	1 (2.7%)
<i>Major complications (treated surgically)</i>	3 (3.9%)	15 (5.9%)	31 (13.4%)	1 (2.7%)
<i>Overall complication rate</i>	5 (6.6%)	25 (9.8%)	67 (29.00%)	2 (5.4%)

Table 9. Complication rates of different synthetic meshes in DTI IBR

In a retrospective review (**Table 9.**) with a mean follow-up of 1.2 years, Tessler et al. revealed a direct material cost savings of \$172,112 over a 10-month period using a synthetic polyglactin 910 (Vicryl®) mesh in DTI BR compared directly to ADM expenses at the authors' institution. The results to date have been encouraging, with excellent aesthetic outcomes. ¹⁷¹

Faulkner et al. retrospectively reported 3-year outcomes (**Table 9.**) and cost savings data using the polyglactin 910 (Vicryl®) mesh with a mean follow-up time of 25.2 months. The cost savings compared to ADMs was greater than \$585,000. However, the authors concluded that obesity and RT may be associated with a higher risk of complications. ¹⁷²

Another alternative to ADMs is the use of a titanium-coated polypropylene mesh (TiLOOP[®] Bra), which was approved in Europe in 2008. A multicentre retrospective study by Dieterich et al. (**Table 9.**) with a mean follow-up of 14 months reported that the TiLOOP[®] Bra had acceptable complication rates and could be a helpful device for DTI BR. No patient-related characteristics presented a significant risk factor for major or minor complications.¹⁷³

In a retrospective analysis, Schrenk (**Table 9.**) reviewed the use of a new, long-term absorbable synthetic material, TIGR[®] Matrix mesh, in 29 patients undergoing 37 mastectomies and DTI BR procedures. After a median follow-up of 18 months, the mean postoperative cosmetic result was rated as 9.1 by patients and 8.3 by breast surgeons on a 10-point scale. Early postoperative results showed no adverse reactions to the mesh and good integration into the tissue, fulfilling many of the desired characteristics and requirements of a matrix in DTI BR.¹⁷⁴

The data from the present retrospective cohort study demonstrate that the use of ULTRAPRO[®] mesh in DTI BR can be safe, feasible, and a low-cost procedure with encouraging aesthetic results. However, due to limitations of this study such as its retrospective nature and the absence of a control group in which ADM was used, the role of the ULTRAPRO[®] mesh in BR should be evaluated in terms of aesthetic outcomes, quality of life, complications and costs in further randomized control trials comparing ULTRAPRO[®] to biological matrices.

According to our findings and statistical analysis, there were no significant correlations between active smoking, BMI, diabetic co-morbidity, cup size or type of incision and the observed complications. As a limitation of the study, the reason could be the statistically low number of patients, especially those with diabetic co-morbidity, active smoking, BMI >25 and large-sized breasts (especially cup size D); however, the study concluded that a history of BCT added a potential risk to DTI BR using ULTRAPRO[®] mesh. According to this and recent reports^{74,138,175} of increased risk in patients with active smoking, BMI >25, co-morbidities (i.e., diabetes), and large-sized breasts (although this was not verified in the present study), patient selection should be considered prior to DTI BR.

6. Conclusions

It is well known that following BCT, the aesthetic results are considered unacceptable in up to 30% of cases due to a relatively large volume loss of the breast, which is the most important factor affecting the final aesthetic outcome.

6.1. According to our findings, with an increasing percentage of excised breast volume, significant deteriorations occurred in the final functional and aesthetic outcomes and quality of life. Similar, significant correlations were revealed between RT and the final aesthetic and functional results.

As a result of the many breast cancer cases in young patients with satisfactory oncological results, the good prognosis and demand for excellent cosmetic results prompted the development of modern breast surgery techniques such as OPS and IBR. However there are relatively few and highly variable objective factors - particularly regarding the maximal tolerable volume loss of the breast - on the point at which conventional BCS are so poor that a woman might have been better served by OPS or mastectomy and BR.

For a given breast, knowledge of the predicted volume loss based on tumor size and the ideal removable volume percentage of each breast quadrant may aid the surgeon in choosing an appropriate surgical technique to achieve acceptable aesthetic and functional results, thereby maintaining a sufficient quality of life.

6.2. Our results reveal that when the resected volume is more than 10% of the entire breast volume in the inner quadrants and more than 15-19% of the volume of the outer quadrants, conventional BCS may not obtain acceptable or good aesthetic and satisfactory quality of life results.

In cases involving a predictably larger volume loss than discussed above and in patients with medium or large breasts, oncoplastic BCS might be a better treatment choice than conventional BCS, whereas patients with small breasts might benefit from mastectomy with BR.

Nowadays beyond the oncological reasons, patients as well as surgeons opt for mastectomy more easily, even in cases of unfavourable location of the tumor, breast-to-tumor volume ratio or genetic disorders. With a current 30-40 % rate of mastectomy – the modern modalities of breast surgery – i.e. postmastectomy IBR has become an accepted approach to

restore the shape and form of the breast and the body image, thereby avoiding the potential drawbacks of mastectomy.

6.3. In line with the international findings, Hungarian data also confirm that although the IBR procedures require a longer operation time they ensure oncologic radicality, do not retard the adjuvant multidisciplinary treatments, allow adequate imaging control. Most patients (89% of our own patients) are satisfied with the cosmetic outcome.

Postmastectomy IBR is a surgical procedure which can be performed safely in appropriate centers. It requires financial background taking into consideration the increasing demand beside the appropriate oncologic and plastic surgical experience. As IBR techniques have become more common, tissue expanders, implants and especially certain biological matrix materials – which are essential parts of DTI IBR - place a significant burden on health care system due to their high cost, especially in developing countries.

6.4. The ULTRAPRO® mesh exhibited encouraging results in DTI BR over a long-term period of evaluation. Our findings indicate that it offers a potentially safe, effective and less expensive alternative to biological matrices for selected patients.

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9. APPENDIX