

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

Ph.D. Thesis

Dávid Pukancsik, M.D.

Supervisors:

Zoltán Mátrai M.D., Ph.D.

Department of Breast and Sarcoma Surgery, National Institute of Oncology,

Miklós Kásler MD, Ph.D., D.Sc., Dr.h.c., FRCS

National Institute of Oncology

University of Szeged, Faculty of Medicine

Doctoral School of Interdisciplinary Medicine

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LIST OF FULL PAPERS THAT SERVED AS THE BASIS OF THE PH.D. THESIS

I. Pukancsik D, Kelemen P, Újhelyi M, Kovács E, Udvarhelyi N, Mészáros N, Kenessey I, Kovács T, Kásler M, Mátrai Z

Objective decision making between conventional and oncoplastic breast-conserving surgery or mastectomy: An aesthetic and functional prospective cohort study.

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II. Pukancsik D, Kelemen P, Gulyás G, Újhelyi M, Kovács E, Éles K, Mészáros N, Kenessey I, Pálházi P, Kovács T, Kásler M, Mátrai Z

Clinical experiences with the use of ULTRAPRO® mesh in single-stage direct-to-implant immediate postmastectomy breast reconstruction in 102 patients: A retrospective cohort study.

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Evaluation of clinicopathological findings and cosmetic outcome of 100 immediate postmastectomy breast reconstruction cases

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OTHER PUBLICATIONS RELATED TO THE THEME OF THE THESIS

I. Mátrai Z., Kunos C., Pukancsik D., Sávolt Á., Gulyás G., Kásler M.

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II. Újhelyi M., Pukancsik D., Kelemen P., Sávolt Á., Gődény M., Kovács E., Udvarhelyi N., Bak M., Polgár C., Rubovszky G., Kásler M., Mátrai Z.

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III. Újhelyi M., Pukancsik D., Kelemen P., Kovács E., Kenessey I., Udvarhelyi N., Bak M., Kovács T., Mátrai Z.

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IV. Pukancsik D., Mátrai T., Kelemen P., Sávolt Á., Újhelyi M., Mátrai Z.

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V. Mészáros N., Major T., Stelczer G., Zaka Z., Mózsai E., Pukancsik D., Takácsi-Nagy Z., Fodor J., Polgár C.

Implementation of image-guided intensity-modulated accelerated partial breast irradiation : Three-year results of a phase II clinical study.
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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.

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). 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. 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%.

Generally, fair to poor cosmetic outcomes following conservative BCS and WBRT are observed in as many as one-third of treated cases resulting in decreased quality of life for the patients. 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. 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. 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.

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). 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) or using local, neighbouring or distant flaps (volume replacement). 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 breast reconstruction (IBR) after mastectomy in wider sense. Presently, nearly 70% of breast cancer cases are eligible for BCS; however, the number of BCS procedures has slightly declined over the last decade. Up to 30% of women may present residual deformity requiring surgical correction after breast-conserving therapy (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. 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.

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 to reach free margins, rejection of radiotherapy (RT), and patient preference (e.g., based on whether they carry the BRCA1/2 gene mutation). 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 and the most important tool of rehabilitation, providing excellent aesthetic outcome and quality of life, avoiding the feared cosmetic drawbacks of mastectomy. 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.

Nowadays the implant-based breast reconstruction (BR) is the most frequent technique following mastectomy in breast cancer and/or BRCA 1/2 mutation carriers. The so-called, two-stage, delayed-immediate BR (D-IBR) accounts for approximately 70% of all reconstructions according to statistics from the American Society of Plastic Surgeons. However, single-stage direct-to-implant (DTI) BR has also become an accepted approach

over the past decade. 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. In addition to the different types of skin-sparing mastectomies (SSMs), the so-called biological matrices (acellular dermal matrices [ADMs]) and other synthetic meshes play key roles in the popularity of DTI IBR. Despite the advantages of ADMs, the related cost of the biological matrices is significant in health care systems. 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.

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 the of 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. Each patient underwent a wide local excision and sentinel lymph node biopsy (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. Subjective aesthetic and functional factors were recorded using the internationally validated Breast Cancer Treatment Outcome Scale (BCTOS). The EORTC Quality of Life Questionnaire was validated in

Hungarian and used to measure the quality of life of breast cancer patients. 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). MRI (magnetic resonance imaging) of the breast was performed to document the oncological status and to calculate the contralateral breast volume. 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.

To evaluate data, a descriptive statistical analysis, Spearman's rank order correlation test, Spearman's Rho statistical analysis, Kruskal-Wallis statistical analysis, receiver operating characteristic (ROC) curves, Friedman's ANOVA test, Mann-Whitney test and Wilcoxon signed-rank test were 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 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. 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, the time of follow-up from the time of surgery in months, and the oncologic status of the patient. 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. 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. Surgeries were performed uniformly according to the institutional oncology protocol, based on the decision of the Multidisciplinary Oncology Committee. The follow-up was performed according to the institutional protocol in every patients. The data were analysed with descriptive and comparative statistical methods.

3.3. The retrospective 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, areola-sparing mastectomy (ASM) or nipple-sparing mastectomy (NSM) followed by single-stage DTI BR using a partially absorbable lightweight ULTRAPRO® mesh. All patients had textured, anatomical or round-shaped Mentor® 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. 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 also recorded, divided into minor and major complications. To record the

palpability of implant borders and the smooth touch of the breast, a 5-point Likert scale (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. The data were evaluated with descriptive statistical analysis, Wilcoxon signed-rank test, Pearson’s chi-square or Fisher’s exact test and multiple regression analysis.

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 axillary lymph node dissection (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, and the mean breast volume was 625.22 cm³. The average percentage of breast volume excised was 14.73%, and the average weight of the excised specimens was 85.58 g. Regarding the breast cancer staging characteristics of the patients, 15 women were pT1spN0(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. 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. 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 ($r=0.684$, $p=0.0001$). 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 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. 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 outcomes 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 with a mean BMI of 23.2. 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 solitary 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. Standard mastectomy (SM) was performed in 14%, SSM in 64%, ASM in 20% and NSM in 2%. 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 latissimus dorsi (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 transverse rectus abdominis muscle (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. The average size of the applied implant was 460 cm³, the filling volume of the expanders was 477 cm³. Early postoperative complication was observed in 18 cases (14,8%). The average time of the initiation of the adjuvant treatment was 4.8 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. 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. Distant metastasis (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/subscapular 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 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. The mean BMI was 23.2. 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. 76 (74.5%) patients had a BRCA 1/2 gene mutation, 11 (6.3%) were active smoker and 8 (4.6%) patients had diabetic-comorbidity. Most of the patients had cup size "B" (45%). 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 ST 0 and 15 ST 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. 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. 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 co-morbidity ($p=1$), 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. 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, whereas the median social functioning score was 83.4. The median score of body image was 83.4. 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.

Recent studies have suggested a high risk of significant defects when 20% of the breast volume is excised, whereas Stevenson et al. found that high risk correlated to the removal of $>12\%$ of the volume. 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. 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). In an older study by Harris et al., 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. 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. 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. 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. With an advances of breast surgery i.e. IBR, the feared consequences of mastectomy could be avoided. 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? 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. 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. According to the current clinical examinations, the IBR did not change the oncologic results, the ratio of LR or the ratio of DM significantly compared with SM. The prognosis of the oncology process – including LR – is principally determined by the biological properties of the tumor, the molecular subtype and the ST of the tumor, which must also be acknowledged in case of the evaluation of surgical treatment. Neither the implant, nor the autologous tissue reconstructions do not influence the timely detectability of the recidives with modern imaging techniques. 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. The IBR did not retard the initiation of the adjuvant treatment in the current retrospective analysis. 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-subscapular position at the same time as the removal of the primary tumor. 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. According to the data of the 3rd National Mastectomy and Breast Reconstruction Audit in United Kingdom, 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. 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. 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 \pm 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. 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. 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 - based on the results of 4.3

Despite the advantages of ADMs, the related cost of the biological matrices is significant in health care systems. The use of synthetic materials in BR is becoming more common as a low-cost alternative to ADMs. 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 \times 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. The present retrospective cohort study showed that DTI BR using ULTRAPRO[®] mesh can provide good aesthetics, 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 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. 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, 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 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. Conclusion

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.

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.

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.

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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