LONG-TERM CLINICOPATHOLOGICAL, COSMETIC AND QUALITY OF LIFE COMPARISON OF ONCOPLASTIC AND CONVENTIONAL BREAST-CONSERVING SURGERY TOWARDS THE STANDARDIZATION OF ONCOPLASTIC TECHNIQUES

Ph.D. Thesis

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

I. Kelemen P, Pukancsik D, Újhelyi M, Sávolt Á, Kovács E, Ivády G, Kenessey I, Kovács T, Stamatiou A, Smanykó V, Mátrai Z.
Comparison of clinicopathologic, cosmetic and quality of life outcomes in 700 oncoplastic and conventional breast-conserving surgery cases: A single-centre retrospective study.
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II. Kelemen P, Pukancsik D, Újhelyi M, Kovács E, Stamatiou A, Ivády G, Kenessey I, Kovács T, Smanykó V, Rubovszky G, Mátrai Z.
Evaluation of the central pedicled, modified Wise-pattern technique as a standard level II oncoplastic breast-conserving surgery: A retrospective clinicopathological study of 190 breast cancer patients.
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III. Kelemen P, Ujhelyi M, Pukancsik D, Sávolt A., Kovács E., Zaka Z., Sándor Zs, Mátrai Z
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1. Introduction

Currently, the breast cancer is the most common malignant disease in women with a gradually increasing incidence and a relatively decreasing mortality rate of 11%. The Hungarian National Cancer Registry recorded 8520 new cases of breast cancer in women, with 2123 deaths in 2017.

1.1 The era of conventional breast conserving surgery

Based on the well known prospective randomized studies of Umberto Veronesi (Milan-I) and Bernard Fisher (NSABP-04) in oncological breast surgery in the last four decades, breast conservation therapy (BCS) has become dominant in the surgical treatment of early stage breast cancers, which is proven to provide survival rates equal to mastectomy if combined with adjuvant whole breast irradiation (WBI) and microscopically negative surgical margin. In practice, the obvious benefits of conventional breast conserving surgery (CBCS) are overshadowed by the fact that in 5% to 30% of the cases, due to microscopically positive surgical margins, a completional surgery (guided reexcision or mastectomy), and in most cases, a 3-5-week-long, logistically demanding radiotherapy is needed, along with impaired cosmetic results or even a distorted breast in 30% of surgical cases. According to an earlier prospective cohort study performed by our working group, the reason for the latter is that the CBCS with adjuvant WBI could cause significant, intolerable cosmetic results for the patients with the loss of 10% total breast volume in the inner quadrants and 15% to 20% in the outer quadrants of the breast when compared to total breast volume. In addition to volume loss, CBCS leaves the tumour bed as an open cavity, thus in the early postoperative period after the absorption of the seroma, the adjacent parenchyma and skin shrinks and is drawn in and adheres to the pectoral muscle or its fascia. As a result a characteristic deformity of the breast can occur usually with a curved scar directly above the tumour, with a decreased volume relative to the contralateral breast and the nipple is pulled away from the axis of the breast mound towards the affected breast quadrant.

1.2 The era of oncoplastic breast-conserving surgery

To overcome the above listed disadvantages of CBCS, sophisticated breast conserving surgeries have been developed with the adaptation of plastic surgical mammoplasty techniques over the last decade, which was named Oncoplastic Surgery (OPS) by Werner Audretsch. The OPS includes the oncoplastic breast-conserving surgery (OBCS), 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. The basis of OBCS is that after radical removal of the tumour, the resulting cavity wound is filled by the mobilisation and transposition of the surrounding tissues (volume displacement) utilising breast ptosis, narrowing the overall base diameter, or footprint, and repositioning the NAC. Alternative to volume displacement is the volume replacement, including the use of local or distant autologous flaps, silicone implants or even autologous fat transfer. These OBCS techniques extend the options for BCS, able to improve aesthetic outcomes, provide higher patient satisfaction and result in better control of tumour margins.

1.3 Techniques and standardization of OBCS

According to Clough's recommendation OBCS can be classified as their technical complexity or volume to be replaced (<20% / 20% to 50%) (Level I. and II. OBCS). Furthermore, the oncoplastic techniques can be related to volume displacement or replacement procedures. Among the procedures available, local flaps, latissimus dorsi myocutaneous flap and reduction mammaplasty/mastopexy techniques are the most commonly used based on the substructural, vascular supply of the breast. The first OBCS techniques were described more than two decades ago. Since then, several OBCS techniques have been developed based on the size and shape of the breast as well as the size and location of the tumour. Even though various detailed classification systems and algorithms have been suggested for use in clinical practice, they achieved neither standardization, nor acceptance on an international level. The lack of standardization of OBCS nomenclature, indication, and outcome assessment challenges the interpretation and comparison of an increasing body of observational evidence. Therefore, standardization of OBCS is necessary for structured education and training, and to plan well-designed, prospective multicenter studies. In general it can be stated that, currently there is still little standardization of OBCS. Further long-term studies needed to provide the OBCS techniques' reproducibility, utility, low interference with the oncologic treatment and higher satisfaction of breast cancer patients.

1.4 Oncological safety of OBCS

According to the First International Consensus Conference on Standardization of OBCS the panelists stated that OBCS increases the risk of complications compared to CBCS. Even though complication rates varied widely among studies, an early complication rate of 20% was commonly described, consisting mostly of delayed wound healing, partial skin necrosis, infection, hematoma, and seroma. Despite the potential impact of complications on the time to adjuvant therapy, virtually all panel members agreed that OBCS does not increase the risk of local recurrence (LR) compared to CBCS. In fact, even though there are no randomized controlled trials, there is an increasingly large body of observational evidence that consistently indicates that OBCS is oncologically safe, even though the length of follow-up is still limited. Concordantly, the largest single-center series published to date revealed no differences in overall and recurrence-free survival between the OBCS and CBCS groups at a median follow-up of 3.4 years. It is essential to know that high level evidence to support the oncological safety and improved aesthetic outcome of OBCS are still lacking, due to most of the current publications' retrospective, multicentric nature using non-standardized OBCS techniques with low number of enrolled patients and short follow-up time. Furthermore, - due to its complexity, - limited data is available of studies that directly compare OBCS and CBCS procedures facilitating the standardization of OBCS techniques.

2. Aims of the thesis

2.1 According to our first hypothesis, the locally standardized (therapeutic mammaplasty, dermoglandular rotation and periareolar) OBCS techniques in line with the CBCS:

a. can provide the adequate oncological safety with low complication rate

b. can provide the radical tumour resection, thus maintaining the local tumour control

c. do not cause delay in initiation of adjuvant therapies

2.2 According to our second hypothesis, the OBCS techniques can provide higher quality of life and aesthetic outcomes with improved satisfaction of the breast cancer patients compared to CBCS.

Revealing the above mentioned hypothesises, the main purpose is to gain wider acceptance of the OBCS techniques.

2.3 According to the third hypothesis, our newly described, modified Wise-pattern OBCS technique:

a. is oncologically safe procedure with low complication rate
b. can provide the radical tumour resection, thus maintaining the adequate surgical margin, and local tumour control

c. can provide improved quality of life and aesthetic outcomes resulting in high patient's satisfaction

Revealing the above mentioned hypothesis, the main purpose is the wider acceptance of the modified Wise-pattern OBCS, thus become a standard oncoplastic technique in any quadrant of the breast.

2.4 According to the fourth hypothesis, our newly described modified Regnault "B" OBCS technique:

a. is oncologically safe procedure with low complication rate
b. can provide the radical tumour resection, thus maintaining the adequate surgical margin, and local tumour control
c. can provide improved quality of life and aesthetic outcomes resulting in high patient's satisfaction
Revealing the above mentioned hypothesis, the main purpose is the wider acceptance of the modified Regnault "B" OBCS, thus become a standard oncoplastic technique of the tumours located in the upper-outer quadrant as the most common location of the breast cancer.

3. Patients and methods

3.1 Long-term comparison of clinicopathologic, cosmetic and quality of life outcomes in 700 oncoplastic and conventional breast-conserving surgery cases

A single-centre retrospective comparative study was performed between January 2010 and January 2017 at the National Institute of Oncology (NIO) in Budapest, Hungary. The study was approved by the Institutional Research Ethics Committee and involved 756 patients with stage 0-III breast cancer. In the investigated period, 378 patients underwent OBCS procedures (the OBCS group). As a control group, patients treated with CBCS (the CBCS

group) were randomly selected during the same period. In cases with breasts that were of moderate or large volume (cup size B/C and greater) or ptotic (Regnault classification type II-III), a therapeutic mammaplasty (central pedicled or modified Wise-pattern, superior and inferior pedicled Wise-pattern) OBCS was performed. In cases with medium or smaller sized (bra cup size B/C) or slightly ptotic breasts (Regnault classification Type I-II, pseudoptosis, parenchymal maldistribution) a dermoglandular rotation (medial, lateral mammoplasty) or periareolar (bra cup size A and greater, Regnault classification normal or Type I) (round block, omega) OBCS was performed. Considering Clough's recommendations, all three aforementioned volume displacement OBCS techniques allowed level I or level II excision if it was necessary. The diagnosis of breast cancer, additional staging examinations and the follow-up of the patients were performed according to the institutional protocol based on that of the European Society of Medical Oncology (ESMO). All the analysed cases underwent whole-breast RT and/or axilla and supraclavicular irradiation if it was necessary. The database included the patients' characteristics, the cliniopathological parameters, the type and initiation time of the adjuvant treatments and the follow-up time. Postoperative complications were divided into two categories. Minor complications included infection treated with antibiotics, haematoma, seroma, and partial skin/NAC necrosis that healed spontaneously. Complications requiring surgical intervention were classified as major complications and included haematoma, chronic infection and seroma (lasting for more than 2 weeks following the removal of the surgical drain), fat necrosis, and partial skin/NAC necrosis. To assess the aesthetic results, a 5-point Likert scale (score: 1, strongly disagree; 2, disagree; 3, undecided; 4, agree; 5, strongly agree) was used. The European Organisation for Research and Treatment of Cancer- Quality of Life Questionnaire (EORTC-QLQ) was applied to measure the quality of life of breast cancer patients at the first postoperative year. To compare the data between the OBCS and CBCS groups, statistical analysis was performed. Statistical significance was accepted when $p<0.05$.

3.2 Evaluation of the central pedicled, modified Wise-pattern technique as a standard level II oncoplastic breast-conserving surgery: A retrospective clinicopathological study of 190 breast cancer patients

A single-institution, retrospective cohort study was performed between February 2011 and January 2017 using a prospective database at the NIO, Budapest, Hungary. The study was approved by the institutional research ethics committee and included 207 stage 0-III breast cancer patients. Patients underwent therapeutic modified Wise-pattern OBCS with immediate

or delayed contralateral symmetrization. The indications for the technique were a moderate or large (cup size B/C or above) and ptotic breast (Regnault classification type II-III, pseudoptosis and parenchymal maldistribution). The technique could provide both level I and level II volume displacement or even extreme OBCS if it was necessary. The diagnosis of breast cancer, additional staging examinations, and follow-up of the patients were performed in accordance with the institutional protocol based on the actual ESMO guidelines. All of the analysed cases underwent whole-breast RT and additional tumour bed boost irradiation and/or axilla and supraclavicular irradiation if necessary. The database included the patients' characteristics, the cliniopathological parameters, the type and initiation time of the adjuvant treatments and the follow-up time. The postoperative complications were divided into two categories. Minor complications that healed spontaneously. Complications requiring surgical intervention were classified as major complications. To assess the aesthetic results, a 5-point Likert scale (1: strongly disagree, 2: disagree, 3: undecided, 4: agree, 5: strongly agree) was evaluated by a committee of 3 breast surgeons. The overall aesthetic outcomes were classified objectively based on photo documentation using the BCCT.core software (version 20) BCCT.core software provided automated measurements using digital marks to establish a 4-point classification scale (1: excellent, 2: good, 3: fair, 4: poor). Collected data were analysed using Statistica 12.0 software. Statistical significance was accepted when $p<0.05$.

3.3 Evaluation of the modified Regnault "B" technique as a standard Level II OBCS. A retrospective clinico-pathological and aesthetic study of 215 breast cancer patients

This retrospective clinicopathological study included 227 stage 0 to stage III breast cancer cases operated with modified Regnault "B" oncoplastic breast conserving technique at the Department of Breast and Sarcoma Surgery of the NIO and was analysed based on a prospectively managed institutional database from March 2012 to October 2018. The study was approved by the institutional research ethics committee. The surgeries were performed mainly on medium and/or large (cup sizes B-D) breasted patients with moderate to severe breast ptosis (Regnault classification Grade II-III, pseudoptosis). The indication for the surgical procedure was Level II OBCS or complete quadrantectomy. Diagnostic tests for breast cancer, imaging tests for staging, required multidisciplinary oncological therapy and follow-up were performed according to the current institutional protocol, which was determined according to the current recommendations of the ESMO and met the recommendations of the 2nd and 3rd Breast Cancer Consensus Conference. Triple-negative, HER2-positive, or higher-risk HER2-negative diseases (>20% Ki67)

indicated chemotherapy. In case of a hormone receptor-positive disease, premenopausal patients were treated with tamoxifen for at least 5 years following surgery. Considering the prognosis, this was supplemented by the use of luteinizing hormone-releasing hormone (LHRH) analogues for 2 to 5 years. The database contained the patients' characteristics, the cliniopathological parameters, the type and initiation time of the adjuvant treatments and the follow-up time. Postoperative complications were classified by the Clavien-Dindo classification. Grade I complications did not require medical or surgical intervention. Grade II complication is a Grade I complication that required medical or surgical intervention. Grade III complications required invasive surgery. During Grade IV complication, a transient organ failure was recorded. Grade V complication occurs when complications lead to death. Patients' quality of life was assessed using the BREAST-Q validated outcome measure, which scored on a scale of 1-100. Higher scores indicated a better quality of life. The subjective aesthetic result was analysed on a 5-point Likert scale (1: strongly disagree, 2: disagree, 3: neither agree nor disagree, 4: agree, 5: strongly agree) evaluated by 3 breast surgeons. The objective aesthetic result was also evaluated using a validated BCCT.core computer program. This software performed automated measurements based on the photo documentation and gave a 4-point rating (1: excellent, 2: good, 3: fair, 4: poor). The results were statistically analysed. Statistical significance was accepted when $p<0.05$

4. Results

4.1 Long-term comparison of clinicopathological, cosmetic and quality of life outcomes in 700 oncoplastic and conventional breast-conserving surgery cases: A single-centre retrospective study

Fifty-six patients were lost to follow-up. In total, 350 breast cancer patients were in the OBCS group, and 350 patients were in the CBCS group. The mean follow-up time was 51 months (range: 12-95 months) for the OBCS group and 52 months (range: 12-96 months) for the CBCS group. The mean age was 58 years (range: 31-85 years) in the OBCS group, while 59 years was in the CBCS group. The groups were homogenous in terms of age, BMI, active smoking status and diabetic comorbidity, while the cup sizes were significantly larger ($p=0.001$) in the OBCS group than in the CBCS group. There were no significant differences between the two groups in terms of the pathological tumour size, tumour grade or invasive

pathological subtype. Compared to the CBCS group, the OBCS group had significantly more patients with pathological Stage II tumours (p=0.035) and more patients with pN1 status (p=0.011). The number of patients with triple negative (p=0.004) and/or highly proliferative tumours (Ki67≥20%) was significantly higher (p=0.001) in the OBCS group than in the CBCS group. Significantly more patients underwent neoadjuvant chemotherapy (p=0.001) in the OBCS group than in the CBCS group. The rates of adjuvant chemo- and biological therapy, RT and endocrine therapy were 40.57%, 100% and 82.85% in the OBCS group and 23.14%, 100% and 87.42% in the CBCS group. There was a significant difference in the number of patients who underwent chemo-and biological therapy between the two groups (p=0.002). Significantly more quadrantectomies were performed in the OBCS group (p=0.001) than in the CBCS group (n=265 vs. n=159), resulting a statistically significant difference (p=0.002) in the number of wide excisions (n=85 vs. n=191), which was the most common technique in standard BCS cases. However, there was no significant difference (p=0.25) between the two groups in the number of ROLL techniques. In the OBCS group, ALND was performed in total of 72 cases, while in the CBCS group, only 18 patients were treated with ALND. Thus, the difference was statistically significant (p=0.001). In relation to the operative times, the OBCS procedures required significantly longer operation times (p<0.01) than the CBCS techniques. The average operation time was 68 minutes for the OBCS group and 58 minutes for the CBCS group. The median weight of the excised specimens in the OBCS group was 90 g (range: 4-529 g), while in the CBCS group, it was found to be 63 g (range: 1.5-878 g) Thus, a significantly larger volume of breast tissue was excised during OPS than during standard BCS (p=0.001). In the OBCS group, the median microscopically tumour-free surgical margin was 8 mm (range: 0-21 mm), while in the CBCS group, it was 4.5 mm (range: 0-17 mm), resulting significantly wider clear surgical margins in OBCS group than in the CBCS group (p=0.010). Due to positive or close surgical margins, 28 (8%) completion surgeries were performed (19 [5.42%] re-excisions and 9 [2.57%] mastectomies) in the OBCS group, whereas in the CBCS group, 38 (10.85%) patients required re-excision and 20 (5.71%) patients needed mastectomies, resulting in a total of 58 (16.57%) reoperations. The rate of completion surgery was significantly higher in the CBCS group than in the OBCS group (p=0.001). There were 11 minor complications (3.14%) and 9 major complications (2.57%) requiring surgical intervention in the OBCS group, resulting in a total of 20 complications (5.71%).In the CBCS group, 23 (6.57%) complications were identified, of which 11 (3.14%) were minor and 12 (3.42%) were classified as major. The overall complication rate was 5.71% in the OBCS group, while in the CBCS group is was

found to be 6.57%. The median time to the initiation of the adjuvant treatment was 4.2 weeks (range: 4-12 weeks) in the OBCS group and 4.1 weeks (4-12 weeks) in the CBCS group. In terms of complication rate and the initiation time of adjuvant therapy, significant differences were not observed between the two groups (p=0.31). During the follow-up period, there were 7 (2.0%) recurrences identified in the OBCS group, 4 (1.14%) of which were local recurrences (LRs) and 3 (0.85%) of which were locoregional recurrences (LRRs). In the CBCS group, 11 (3.14%) LRs and 2 (0.57%) LRRs with distant metastasis were identified, resulting in a total of 13 (3.71%) recurrences. There were no statistically significant differences between the OBCS and the CBCS groups regarding the rates of LR (p=0.29), LRR (p=0.31) and distant metastases (p=0.33). Two patients in the CBCS group were not alive at the time of the last follow-up due to the progression of the disease. The median values of the aesthetic outcome score were significantly different between the two groups, with 4.4 points (range: 3-5) in the OBCS group and 3.2 points (range: 1-5) in the CBCS group (p=0.001). In the OBCS group, the median value of the emotional functioning score was 91.6 (range: 50-100), whereas the median social functioning score was 83.4 (range: 33-100). The median body image score was 91.6 (range: 50-100). In the CBCS group, the median value of the emotional functioning score was 83.4 (range: 50-100), whereas the median social functioning score was 75.0 (range: 50-100). The median body image score was 75.0 (range: 33-100). All the median scores of the aesthetic outcomes were significantly higher (p<0.01) in the OBCS group than in the CBCS group.

4.2 Evaluation of the central pedicled, modified Wise-pattern technique as a standard level II oncoplastic breast-conserving surgery: A retrospective clinicopathological study of 190 breast cancer patients

Seventeen patients were lost to follow-up. As a result, a total of 190 patients were enrolled and underwent therapeutic modified Wise-pattern OBCS. In 112 patients, immediate contralateral symmetrization was performed, while this procedure was carried out in a second stage in 74 patients. Four patients underwent therapeutic OBCS on both sides. The mean follow-up time was 43.9 months (range: 12-72 months). The mean age of the patients was 56 years (range: 31-78 years). The mean BMI was 24.2 kg/m^2 (range: 17.9-34.4). Fifteen patients were active smokers, and 8 had diabetes as a co-morbidity. The vast majority of the patients had pT1a-c (42.9%) pTN0 (58.1%) tumours. A total of 12.6% of the patients underwent neoadjuvant chemotherapy. The rates of adjuvant chemo- and biological therapy, RT and endocrine therapy were 43.7%, 100% and 85.5%, respectively. Furthermore, 68 patients

received additional boost irradiation. The mean weight of the excised specimens was 129.8 g (range: 16-533 g), and the mean pathological tumour size was 18.37 mm (range: 5-60 mm). The median microscopically free surgical margin was 7 mm (min.-max.: 0-19 mm). Due to positive or close surgical margins, 11 (5.78%) re-excisions and 2 (1.05%) mastectomies were performed, resulting in 13 (6.84%) reoperations in total. In total, 45 complications (12.9%) were recorded, including 33 minor (9.4%) and 12 major (3.4%) complications requiring surgical intervention. The median time until the initiation of the adjuvant treatment was 4.9 weeks (range: 4-12 weeks). In the follow-up period, 11 (5.8%) recurrences were identified, 6 (3.2%) of which were LR, 3 (1.6%) of which were LRR, and two (1.05%) of which were a LRR with distant multiplex bone metastasises. The DFS and the OS rates were found to be 75.5% and 98.7%, respectively. Two patients were not alive at the time of the last follow-up due to the progression of the disease. The majority of the breast surgeons agreed with the statement "This case has an excellent aesthetic outcome", with a mean score of 4.1 (range: 1.8-5). Evaluating the objective outcome by BCCT.core, the median value of the overall aesthetic outcome was 1.9 (range: 1-4). The mean operative time for bilateral cases was 119 minutes (range: 92-185) with SLNB or ALND. The cases without contralateral symmetrization required a mean of 69 minutes (range: 42-102) with SLNB or ALND.

4.3 Evaluation of the modified Regnault "B" technique as a standard Level II oncoplastic breast-conserving surgery. A retrospective clinico-pathological and aesthetic study of 215 breast cancer patients

Of the 227 patients, 215 patients' data have been analysed, 12 patients were excluded from the study due to missing data. Patients' mean age was 53 years (range: 29-81 years). Median follow-up period was 47 months (range: 7-85 months). PST was administered in 29 cases (13.5 %). 22 patients declared themselves as active smokers, and 11 patients had diabetes in their medical history. The vast majority of the patients had pT1a-c (38.1%) pTN0 (70.2%) tumours. The mean BMI was 23.9 kg/m^2 (±6.4). The rates of adjuvant RT and endocrine therapy were 98.1%, and 84.7%, respectively. The mean weight of the excised specimens was 49.8 (13.4-149.9), and the mean pathological tumour size was 30 mm (±13). Positive surgical margins lead to re-excision in 13 cases (6%), and mastectomy in 3 cases (1.4%). Total recurrence rate was 4.7% (n=10) including 4 cases (1.9%) of LR, 3 cases (1.4%) of LRR and 3 cases (1.4%) of distant metastases during the assessed time period. One patient died of distant metastases (0.4%). Subjective aesthetic outcome reached 4.2 points on the Likert scale (range: 2-5). Breast surgeons mostly agreed uniformly with the excellent

aesthetic result. Based on BCCT.core software, the mean value of objective aesthetic outcome was 1.3 points (range: 1-4 points). According to BREAST-Q questionnaire the mean result of "satisfaction with the appearance of the breast", "discomfort caused by RT", "psychosocial well-being", "physical well-being" and "sexual well-being" were rated 90, 78, 87, 78 and 60 points, respectively. Total complication rate was 11.2% (n=24). Grade I complications were detected in 12 cases (5.6%) (lymphoedema 7 (3.3%), seroma 3 (1.4%), suffusion 1 (0.4%), impaired wound healing 1 (0.4%)), Grade II complications were detected in 7 cases (3.3%) (chronic seroma 3 (1.4%), impaired wound healing 2 (0.9%), inflammation 2 (0.9%)), and Grade III complications were detected in 5 cases (2.3%) (haematoma evacuation 3 (1.4%), inflammation 2 (0.9%)). Grade IV and Grade V complications were not observed. Median time interval between surgery and initiation of adjuvant therapy was 5 weeks (minimum 4, maximum 12 weeks). Total surgery time was 47 minutes (35-85 minutes) including axillary surgery.

5. Discussion

5.1 Comparing the clinicopathological, cosmetic and quality of life outcomes of oncoplastic breast conserving surgery to conventional one - based on the results of study 4.1

High level evidence to support the oncological safety and improved aesthetic outcome of OBCS are still lacking, thus there is little standardization of OBCS, which makes the scientific comparison of the techniques among each other and to CBCS challenging. In this retrospective analysis, the results of the therapeutic mammaplasty, the periareolar and the dermoglandular rotation OBCS procedures were compared to the outcomes of CBCS according to the following five clinico-oncological parameters. In this study, significant differences were not observed in the rates of LR and LRR between the OBCS and CBCS groups, which had total recurrence rates of 2.0% and 3.71%, respectively. Recent studies with follow-up intervals of 3, 3–5 and 5 years had mean LRs of 1.7, 3.7, and 6.0% and distant metastases rates of 3.8, 7.1, and 11.9%, respectively. The main advantage of OBCS techniques seems to be the ability to perform wider excisions without compromising the aesthetic outcomes, while reducing the risk of positive margins. Our results revealed that the excised weight of the specimens was significantly larger in the OBCS group than in the CBCS group (90 g vs. 63 g), even though there was no significant difference in pathological grade in

the two groups. The explanation for the larger excised specimens in the OBCS group could be the significantly higher number of patients who underwent neoadjuvant chemotherapy with unfavourable biological tumour subtypes and larger initial clinical tumour sizes. Thus, the extended radicality of OBCS may result in the overtreatment of some breast cancer patients; however, in our study, significantly wider microscopically tumour-free margins (8 mm vs. 4.5 mm) and a lower rate of completion surgeries due to positive surgical margins were found in the OBCS group compared to the CBCS group (n=28 [8.0%]) vs. n=58 [16.6%]).

A recent publication by Carter et al. showed a lower rate (5.8%) of positive or close margins after OBCS than after CBCS (8.3%).

Down et al. found a significantly lower need for re-excision after OBCS (37 patients) than after CBCS (121 patients) (5.4% vs. 28.9%). Among studies that reported oncologic outcome data for OBCS procedures, the crude OS and DFS rates were 95.0 and 90.0%. In line with the international results, our findings showed an OS rate of 100.0% and a DFS rate of 88.5% for patients who underwent OBCS, while in patients who underwent classic BCS, the OS and the DFS rates were found to be 97.3 % and 78.2%, respectively. The groups did not differ in terms of the observed survival rates. According to our data, OBCS does not seem to increase morbidity compared to CBCS; moreover, the rate of complications was slightly higher in the CBCS group (6.5%) with the most common complication of seroma formation, found in 2.6% of the cases. In the OBCS group, complications occurred in 5.7% of the cases, and the most common complication was infection, which occurred in a total of 2.3% of the cases.

A recent large systematic review by De La Cruz et al. involving 6011 breast cancer patients demonstrated no statistically significant difference in the incidence of postoperative complications among women undergoing oncoplastic and non-oncoplastic lumpectomies. Therefore, oncoplastic reconstruction at the time of BCS does not appear to significantly increase the risk of postoperative complications that would delay initiation of adjuvant therapy. The median time to the initiation of adjuvant treatment was almost the same in the OBCS and CBCS groups (4.2 weeks vs. 4.1 weeks). In the OBCS group, our results were in line with those of the majority of the current publications, showing no delay in the time to the initiation of adjuvant treatments due to complications.

A meta-analysis of 61 publications comparing 3165 patients after OBCS with 5494 patients after CBCS showed that satisfaction with the aesthetic outcome was higher in the OBCS group than in the CBCS group (89.5% vs. 82.9%, $p<0.001$) In a prospective study,

Veiga et al. demonstrated significantly higher quality of life outcomes in the OBCS group than in the CBCS group. At the 1st postoperative year, the results of the EORTC questionnaire rated by the patients showed that all median values for the quality of life outcomes (emotional functioning, social functioning, body image) were greater than 83.4 points, representing a high quality of life in the OBCS group that was significantly better than that of the CBCS group. In the CBCS group, the vast majority of the patients rated their quality of life parameters near 71.2. According to our data, patients who underwent OBCS had higher median aesthetic outcome scores than the patients treated with CBCS (4.4 vs. 3.2 points).

According to a recent publication, patients who underwent wide local excision required significantly shorter operation times than those patients who underwent OBCS (62 minutes vs. 91.4 minutes).

In a prospective cohort study by Clough et al., out of 101 OBCS cases, 89 patients underwent immediate contralateral symmetrisation, with a mean operation time of 2 hours. In the present study, even without immediate contralateral symmetrisation, the OBCS cases required significantly (10 minutes) longer operative times than the CBCS cases.

5.2 Assessing the clinipathological, cosmetic and quality of life outcomes of the central pedicled, modified Wise-pattern oncoplastic technique - based on the results of study 4.2

TM in ptotic or moderate- or large-breasted patients is a versatile technique allowing the removal of tumours in almost every quadrant of the breast with improved cosmetic results and similar five-year survival and local recurrence rates to those of conventional breast-conserving surgery. Few studies have investigated the role of the central pedicled Wise-pattern technique in OBCS. The present study aimed to facilitate the repeatability, utility of the modified Wise-pattern technique in volume-displacement OBCS, thus becoming a standard oncoplastic technique and gaining wider acceptance. In this study, with a mean follow-up of 43.9 months, the overall recurrence rate was found to be 5.8%, which does not differ significantly from those of the classic TM techniques. Kronowitz et al. reported a 5% LR rate after a mean follow-up of 36 months, while a slightly lower rate (2%) was found by Losken after a mean follow-up of 40 months using the classic, dermal pedicled TM techniques. The ability to perform a large partial mastectomy thanks to TM oncoplastic techniques in reconstructing the breast allows for lower positive margin rates reported to be in 10% to 12% range in several large review studies. Our data showed that the mean free surgical margin was 7 mm, which could explain the low re-excision (5.8%) and mastectomy rates (1.1%) due to positive or close surgical margins. In a recent published meta-analysis, the

average complication rate in the oncoplastic reduction mammaplasty group was 16% and do not cause a significant delay in the initiation of adjuvant treatments. In accordance with the data of current studies, the median time to the initiation of adjuvant treatments was 4.9 months. Therefore, a delay in adjuvant treatments was not verified. The overall complication rate was 12.9%. A majority of the complications were classified as minor and healed spontaneously using conservative treatments. The most common complication was skin redness, a clinical sign of lymphoedema, with a rate of 3.1%. The satisfaction and aesthetic outcomes are reportedly very high in patients treated with TM. In the publication of Chang et al., 70% of the patients who underwent TM rated the final cosmetic result as excellent. Our data demonstrate that the majority of the breast surgeons agreed with the statement "This case has an excellent aesthetic outcome", with a mean score of 4.1. In addition, the median overall objective outcome score was 1.9. Both the subjective and objective aesthetic results represented an improved cosmetic outcome when the modified Wise-pattern OBCS was applied. The only drawback of the TM seems to be the longer operative time, in which concomitant contralateral symmetrization could be an important factor. Nos et al. reported the mean operative time as 150 minutes, including ALND and symmetrization of the contralateral breast. Here, the mean time in bilateral cases was 119 minutes with SLNB or ALND. The cases without contralateral symmetrization required a mean time of 69 minutes with SLNB or ALND.

5.3 Assessing the clinipathological, cosmetic and quality of life outcomes of the modified Regnault "B" oncoplastic technique - based on the results of study 4.3

No paper has been published on BCS as modified volume-displacement level II oncoplastic OBCS technique described by Regnault P in 1974, and presented by the authors. Existing publications only refer to breast reduction. In this paper the authors present the detailed surgery description of modified Regnault "B" level II OBCS technique and associated clinicopathological assessment for the first time. Data were compared to the outcome of other level II OBCS techniques. The Regnault "B" OBCS technique can be applied safely for BCS of medium-sized or large breasts with minimum 20% and maximum 50% volume loss. In addition to an excellent aesthetic outcome, the presented technique does not increase LR rate compared to CBCS. According to our study, tumour recurrence was observed in 4.7% of all cases during follow-up period of 47 months, which does not differ from 5% recurrence rate during 36 follow-up period presented by Kronowitz et al. OBCS techniques have the advantage of less positive surgical margins. Based on the study published

by McIntosh et al, the rate of completion surgeries was 7.2% which also corresponds to the outcomes of our study showing a rate of 7.4%. In our study the rate of completion re-excision/mastectomy (6% vs 1.4%) was higher than in the study of McIntosh (3.5% vs 3.7%). Based on literature data, the frequency of complications with therapeutic breast reconstruction may be 0% to 36% which will not delay significantly the start of adjuvant therapy. According to our study, the median interval between surgery and initiation of adjuvant treatment was 5 weeks corresponding to published international outcomes. Total complication rate was 11.2% based on study data. Grade I complications were the most frequent and healed spontaneously in most cases. The most common complication was lymphoedema with erythema of the breast (3.3%). Surveys regarding therapeutic breast reconstruction surgery report high level of patient satisfaction. Chang et al. reported in their study "excellent" aesthetic outcome after therapeutic breast reconstruction in 70% of cases. According to our results, a mean value of 4.1 points on the subjective aesthetic Likert scale corresponds to the statement that "the Regnault B OBCS technique provides excellent aesthetic outcome", which is confirmed by an average objective value of 1.3 on BCCT.core which also corresponds to an "excellent" rating. As it does not require any symmetrisation, the average surgery time was 47 minutes which does not increase surgery time significantly compared to CBCS. The surgical technique has the disadvantage that in case of a completion mastectomy incisions on the skin envelope make an immediate reconstruction difficult.

6. Conclusions

In general it can be stated that high level evidence to support the oncological safety and improved aesthetic outcome of OBCS are still lacking, thus currently there is still some standardization of OBCS. It is essential to provide more long-term studies regarding the reproducibility, utility, low interference of OBCS techniques with the oncologic treatment and higher satisfaction of breast cancer patients facilitating the standardization of the oncoplastic techniques.

6.1 Our results revealed that the investigated volume displacement OBCS techniques (therapeutic mammaplasty, dermoglandular rotation and periareolar) in line with the CBCS technique:

a. are able to provide the expected oncological safety with low morbidity
b. can provide the local tumour control with radical tumour resection, reducing the rate of re-excision and completion mastectomies
c. do not cause delay in initiation of the adjuvant therapies

6.2 Our results revealed that the OBCS techniques allow the removal of large volumes of breast tissue with improved cosmetic and quality of life outcomes providing higher satisfaction of the breast cancer patients compared to CBCS cases.

Additionally it should be stated that, the aforementioned OBCS techniques required longer operation times than the CBCS. Furthermore, the extended radicality of OBCS could reduce the rate of re-excision and completion mastectomies, although it may result in overtreatment of some breast cancer patients, highlighting the importance of appropriate patient selection for OBCS.

6.3 Our results revealed that the "modified" Wise-pattern OBCS technique out team first presented in the international literature:
a. is a safe and reproducible volume-displacement OBCS in ptotic and moderate- or large-breasted patients with a low and acceptable complication rate
b. is able to minimize the rate of positive surgical margins, providing radical level II resections, thus the adequate local tumour control
c. can provide the immediate symmetry and improve the aesthetic and quality of life outcomes contributing to the satisfaction of breast cancer patients

The "modified" Wise-pattern OBCS could be a standard level II oncoplastic technique of T1-T3 tumours allowing real anatomic uni- or even bi-quadrantectomy resections from the periphery of the parenchyma up to the retromammary space in a "slice of cake" manner for solitary or multicentric tumours in any quadrant (even the central) of the breast.

Additionally, it should be noted that the "modified" Wise-pattern technique requires the symmetrisation of contralateral breast resulting in longer operation time.

6.4 Our results revealed that the "modified" Regnault B OBCS technique which technique out team was the firs present in the international literature:

a. is a safe and repeatable volume-displacement OBCS technique in ptotic and medium- or large-breasted patients with low complication rate

b. is suitable for removing 20% to 50% of breast parenchyma providing adequate surgical margins thus maintaining the local tumour control

c. able to provide high level of patient satisfaction and cosmetic outcomes with improved quality of life

The "modified" Regnault B OBCS could be a standard level II oncoplastic technique of T1-T3 tumours located in the upper-outer quadrant as the most common location of breast cancer.

The "modified" Regnault B OBCS technique has the advantage that it does not require contralateral symmetrisation surgery, while its disadvantage is that in case of completion mastectomy, incisions made on the skin envelope of the breast make immediate reconstruction difficult but do not exclude it.

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