EVALUATION OF ADVANCED CLINICPATHOLOGICAL AND STRUCTURAL ASPECTS OF MODERN ONCOPLASTIC BREAST CANCER SURGERY

Ph.D. Thesis

Bence Dorogi, M.D.

Supervisor:

habil. Zoltán Mátrai M.D., Ph.D.

Department of Breast and Sarcoma Surgery

National Institute of Oncology

University of Szeged, Faculty of Medicine

Doctoral School of Interdisciplinary Medicine

Szeged

2022

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

I. Dorogi B, Bukovszky B, Mátrai T, Sávolt Á, Polgár Cs, Kelemen P, Kovács T, Rényi-Vámos F, Ivády G, Kovács E, Téglás T, Kásler M, Mátrai Z.

Mapping of the functional anatomy of lymphatic drainage to the axilla in early breast cancer: A cohort study of 933 cases.
Eur J Surg Oncol. 2019 Feb; 45(2):103-109. doi: 10.1016/j.ejso.2018.08.030. Epub 2018 Oct 7.
IF: 3.959

II. Dorogi B, Újhelyi M, Kenessey I, Ivády G, Mátrai Z.

Clinicopathological correlations of areola-sparing mastectomies versus nipple-sparing mastectomies: Analysis of the oncological and cosmetic importance of the components of the nipple-areola complex
Breast J. 2020 Oct; 26(10):2081-2086. doi: 10.1111/tbj.13957. Epub 2020 Jul 1.
IF: 0.000

III. Dorogi B, Mátrai T, Újhelyi M, Kenessey I, Kelemen P, Sávolt Á, Huszár O, Ping O, Pukancsik D, Mátrai Z.

Assessing the needs of Hungarian breast cancer patients for modern oncoplastic breast surgical treatment – questionnaire study of 500 patients.
Orv Hetil. 2020 Jul;161(29):1221-1228. doi: 10.1556/650.2020.31768.
IF: 0.540

∑ 4.499

OTHER PUBLICATIONS RELATED TO THE THEME OF THE THESIS

I. Dorogi B, Gulyás G, Kunos Cs, Udvarhelyi N, Mátrai Z.

Contralateral axillary silicone lymphadenopathy after modified radical mastectomy and reconstruction.

Eur J Plast Surg. 2014 Jun; 37:505–508. doi: 10.1007/s00238-014-0970-4.
IF: 0.000

II. Mátrai Z, Tóth L, Saeki T, Sinkovics I, Godény M, Takeuchi H, Bidlek M, Bartal A, Sávolt A, **Dorogi B**, Kásler M.

The potential role of SPECT/CT in the preoperative detection of sentinel lymph nodes in breast cancer.
Orv Hetil. 2011 Apr;152(17):678-88. doi: 10.1556/OH.2011.29077.
IF: 0.000

III. Dorogi B, Pálházi P.

Az emlő és a regionális nyirokelvezetés anatómiája
In: Mátrai Z, Gulyás G, Kásler M: Az emlőrák korszerű sebészete
Medicina, Budapest, 2015; 39-47.
IF: 0.000

∑ 0.000

1. Introduction

Breast cancer is the most common malignancy in women with more, than 8.400 newly diagnosed cases and nearly 2.200 deaths in 2017 in Hungary, according to the Hungarian National Cancer Registry. Breast cancer treatment has gone through a long evolutional process from Halsted's procedure to nowadays' complex multidisciplinary approach and oncoplastic surgical procedures on the last decades.

With the scientific endorsement of oncoplastic breast surgery, the main focus of breast cancer treatment shifted to treatment optimization by applying tailored de-escalation or escalation of the current protocols. Our aim in this dissertation was to evaluate the following yet not sufficiently studied issues related to modern breast surgery.

A better understanding of the associations between the lymphatic drainage pattern of the breast tumour with its clinicopathological features may provide further basic information for the interpretation of American College of Surgeons Oncology Group (ACOSOG) Z0011, Optimal Treatment Of the Axilla – Surgery or Radiotherapy (OTOASOR) and After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trials and could have particular importance in determining whether axillary lymph node dissection (ALND) can be safely omitted.

The cosmetic role and oncologic importance of the nipple-areola complex (NAC) and its components in the context of the preservation of the complex anatomical unit of the nipple by nipple-sparing mastectomies (NSM) or only the pigmented skin of the areola by areola-sparing mastectomies (ASM) could provide useful scientific data in the selection of the appropriate surgical and reconstruction technique in cases requiring mastectomy.

As a consequence of the rapid spread of modern oncoplastic breast surgery in the recent decades, the resulting demand for breast reconstruction not only poses a challenge for breast and plastic surgeons, but also raises a number of system-related issues in all European countries. Recognizing and analysing the needs and expectations of the Hungarian breast cancer patients about a modern oncoplastic health care system forms the basis of approaching today's yet understudied questions, the needs and requirements of the Hungarian health care system to meet the rapidly expanding need for oncoplastic breast surgery.

2. AIMS

1. Studying the location of the SLNs according to the axillary anatomical subregions and assessing the relationship between that and the clinicopathological characteristics, molecular subtype and location of the primary tumour by breast quadrants in order to characterize their functional and morphologic lymphatic drainage pattern

2. Assessing the coverage of the axillary nodal subvolumes by standard and high tangential fields (STgF and HTgF) during whole breast irradiation (WBI)

3. Based on our SLN mapping findings, comparing the SLN positivity rate in the studied anatomical subregions with the respective data from the literature gained by the ARM technique

4. Comparison of the oncological and cosmetic outcome after ASM and NSM

5. Collecting the opinion and expectations of Hungarian women with breast cancer regarding modern oncoplastic health care system

3. PATIENTS AND METHODS

3.1. Mapping the sentinel lymph nodes in the anatomical axillary subregions: a retrospective cohort study

This study - registered on Clinicaltrials.gov (identifier: NCT01804309) and approved by the Institutional Ethics Committee Board - was performed between March 2013 and February 2015 at the NIO, Hungary. Female patients older than 18 years were eligible with primary unilateral invasive or microinvasive, clinically lymph node-negative early-stage breast cancer (cT0-2N0M0) needing SLNB. Exclusion criteria included previous ALND, cN1-2, pregnancy, lactation and necessity of neoadjuvant treatment for breast cancer.

The complex oncological therapy was performed according to the actual international guidelines adopted by the NIO and was not different from those who were not included in the trial. Radiopharmaceutical (80 Mbq 99m Tc labelled nanocolloid, particle size: 50-800 nm) was injected to the intratumoural area or periareolar tissue on the day before surgery. If the

lymphoscintigraphy was unsuccessful, 2-3 ml of periareolar Patent blue 25 mg/ml® dye injection was applied 10 minutes before the operation.

Patients then underwent a wide excision or mastectomy and axillary sentinel lymph node biopsy (SLNB) followed by ALND instantly if the SLN was positive by intraoperative imprint cytology or as a second operation if the SLN was positive only by histological examination. If isolated tumour cells or micrometastases were found in the SLN, ALND was omitted.

The subregional localisation of the SLN(s) was identified and recorded on a standardised data sheet by the operating surgeons immediately after biopsy in the operating theatre. Postoperatively, all the removed lymph nodes were meticulously examined by the pathologists according to the guidelines.

Following breast-conserving surgery, all patients had 3D-conformal radiotherapy (RT). Breast irradiation was given via STgFs. The STgF upper margin was generally the base (± 1 cm) of the clavicle. Retrospectively, for the purpose of this study in 61 randomly selected node-positive patients treated with breast-conserving therapy in whom the SLNs were found in the anterior or posterior axillary subregions (Level I), HTgFs were simulated using the same CT data. HTgF consisted of a superior border placed at the inferior edge (or below maximum 2 cm) of the humeral head. Before RT planning, axillary volumes (Levels I, II and III) were contoured using the Radiation Therapy Oncology Group (RTOG) contouring atlas. Coverage of the axillary volumes by tangential fields was classified according to the tangential field target volumes (Levels I, II and III) overlap: 100% overlap (complete coverage), <100% overlap (partial coverage), and 0% overlap (lack of coverage: out of field).

Multiple studies were conducted to analyse the feasibility and oncological safety of the ARM technique, however only a few authors focused on the detailed anatomical localisation of the ARM nodes. A review of the literature was performed and two studies were selected to analyse and compare the subregional localisation and positivity rate of SLNs of our study with the subregional localisation and positivity rates of ARM lymph nodes.

3.2. Comparison of oncological and cosmetic outcome after areola-sparing mastectomy versus nipple-sparing mastectomy: analysis of a prospectively collected database

This single-centre retrospective comparative study was performed between April 2013 and December 2018 at the NIO, based on the prospectively led institutional database. All female patients for whom the multidisciplinary team decided mastectomy with delayed-immediate implant-based breast reconstruction were eligible. Exclusion criteria included nipple involvement, inflammatory breast cancer, previous breast surgery, pregnancy and lactation.

The diagnosis of breast cancer, additional staging examinations, adjuvant treatments, and follow-ups were performed according to an institutional protocol based on the European Society of Medical Oncology (ESMO) and on the European Society for Radiotherapy and Oncology (ESTRO) guidelines.

The procedures in both groups were performed by the same qualified breast surgeons (having European Board of Surgery Qualification (EBSQ) license), based on the decision of the breast multidisciplinary team with the same delayed-immediate implant-based breast reconstruction techniques. SLNB was performed for axillary staging. If the SLN was positive, based on the decision of the multidisciplinary team either ALND was done as a second operation or in selected cases (when postmastectomy radiotherapy (PMRT) was indicated for T3-T4 tumours) axillary and supraclavicular radiation fields were applied to treat the axilla. PMRT in node-positive patients was always recommended for high-risk patients with one to three positive axillary lymph nodes, or involved resection margins, four or more involved axillary lymph nodes and T3–T4 tumours independent of the nodal status.

Postoperative complications were assessed by applying the Clavien-Dindo classification system. For the assessment of the aesthetic outcomes, a 5-point Likert scale was applied. The BREAST-Q validated patient-reported outcome measure (PROM) reconstruction module version 2.0 postoperative questionnaire was applied to measure the quality of life (QoL) of the patients.

3.3. A survey on the needs of Hungarian breast cancer patients regarding modern oncoplastic breast surgery

This study was conducted enrolling 500 patients who underwent mastectomy and the breast reconstruction was either done at the same time as the removal of the primary tumour (immediate) or was started (e.g. by implantation of a tissue expander) and completed in the second session (delayed-immediate breast reconstruction) between January 2015 and December 2017 at the NIO.

The diagnosis of breast cancer, additional staging examinations, adjuvant treatments and follow-ups were performed according to the current international guidelines applied by the NIO. The operations were performed by experienced and internationally qualified breast surgeons (having the EBSQ license) and plastic surgeons based on the decisions of the institutional multidisciplinary team.

Questionnaires were distributed to patients the day before breast surgery and were completed voluntarily and anonymously prior to the intervention. Following questions on age, highest level of education, and marital status, the questionnaire contained eleven structured questions to measure the emotional and mental condition and attitudes related to the loss and reconstruction of breast, the expectation of cosmetic outcome, the qualification of the operating surgeon and the patient's demand for the health care system and funding.

3.4. Statistical analysis

For the study of mapping the sentinel lymph nodes in the anatomical subregions of the axilla, all the collected data were registered in the institutional database and the relationships between SLN localisation, breast tumour localisation, histopathological characteristics and radiopharmaceutical injection sites as well as the comparison of the RT coverage fields were statistically analysed using the Fisher's exact and Pearson's chi-square tests.

For the retrospective comparative study of ASM and NSM the type and initiation time of the adjuvant treatments, postoperative complications, follow-up times, oncologic status of the patients, aesthetic results (a 5-point Likert scale) and postoperative patient satisfaction (BREAST-Q) were all assessed and analysed using Mann–Whitney U, Fisher's exact and Pearson's chi-square tests and Kaplan-Meier method.

For the survey on the needs of Hungarian breast cancer patients, all the answers were statistically analysed in the context of marital status and educational level applying the Fisher's exact and Pearson's chi-square tests.

4. RESULTS

4.1. Mapping the sentinel lymph nodes in the anatomical axillary subregions: a retrospective cohort study

A total of 933 women were enrolled in the study and 63 patients were excluded due to breast tumour larger than 5 cm (n=3), newly discovered lympho-proliferative disorders (n=2) or uninterpretable sentinel data sheet or incomplete clinical-histological data (n=58). As a result, a total of 870 patients' data was analysed.

A statistically significant heterogeneity was found regarding the location of the breast tumour and its molecular subtype (p=0.035).

We also analysed the distribution pattern and metastatic status of the SLN in the subregions of the axilla. The most common site of the SLN was the anterior subregion (39.8%; n=346), while the least common was the apical subregion (3.4%; n=30). In contrast, the positivity rate was higher in the apical subregion (30.0%; n=9) than in the anterior subregion (21.1%; n=73). The SLN was present in the lateral subregion in 5.6% (n=48) of the cases. Of these 48 lymph nodes, 11 SLNs were positive (22.9%). In the central and posterior subregions, 53 and 43 SLNs, respectively, were found to be positive out of the 244 (21.7%) and 202 (21.3%) removed lymph nodes, respectively. In 96.6% (n=840) of the cases, the SLN appeared in the anterior, posterior, lateral or central subregions, corresponding to the Level I and II zones.

None of the examined characteristics of the primary breast cancer (molecular subtype p=0.360) had significant relationship with the subregional localisation of the SLN.

In case of intratumoural application, we found significant relationship between the situation of the breast cancer and the subregional location of the SLN (p=0.016)

According to our data, tumours in the upper-outer quadrant are most frequently drained to the anterior subregion (34.2%). Posterior subregion receives lymph mainly from the upper-outer quadrant (31.6%) and the axillary process (36.3%), whereas the inner and central

quadrants have very similar drainage patterns with a tendency to give efferent lymphatics more often to the anterior (53.9%, 69.6% and 54.5%) and central (28.8%, 26.1% and 22.7%) lymph nodes. The central lymph nodes receive lymphatic drainage equally from the different quadrants of the breast.

In 548 (63.0%) patients, the SLN was located within the anterior or posterior subregions (Level I). 116 of them (21.2%) had axillary lymph node metastasis, out of whom 83 (15.1%) were treated with RT in our Institute. There was a significant difference between the STgF and HTgF plans regarding the coverage of the Level I axillary region. HTgF increased the rate of cases with level I axillary region complete coverage from 0% to 65.6% (40 of 61; $p<0.0001$). Concerning the Level II volume, the rate of complete coverage with STgF or HTgF was 0% and 6.6% (4 of 61), respectively ($p=0.1198$). The rate of "out of field" cases was very high with STgF, 72.1% (44 of 61), but "out of field" cases were not observed with HTgF irradiation ($p<0.0001$). The coverage of the Level III volume was very poor (rate of "out of field" with STgF or HTgF: 91.8% and 9.8%, $p<0.0001$).

We also analysed and compared the subregional localisation and positivity rate of SLNs of our study with the subregional localisation and positivity rates of ARM lymph nodes described in the studies of Ikeda et al. and Bedrosian et al. Summarizing the results, the least common SLN subregions (i.e. the lateral and apical subregions) seem the most common sites for the ARM lymph nodes. Regarding positivity, both studies selected from the literature found metastatic lymph nodes exclusively in the lateral and apical subregions, where we detected the highest positivity rates (22.9% and 30.0%, respectively).

4.2. Comparison of the oncological and cosmetic outcome after areola-sparing mastectomy versus nipple-sparing mastectomy: analysis of a prospectively collected database

Out of the 251 selected cases (ASM: n=147; NSM: n=104), eight patients (ASM: n=5; NSM: n=3) were excluded from the study due to loss of follow-up or incomplete clinicopathological data; eleven women (ASM: n=6; NSM: n=5) from both groups were excluded because of previous breast surgery, and five patients (ASM: n=2; NSM: n=3) were omitted from further evaluation because of positive nipple-areola margins requiring NAC

resection. As a result, a total of 134 and 93 patients were included having had ASM and NSM, respectively.

There was no significant difference in duration of the surgical procedures between the two groups (p=0.431). The median time of ASM was 80 minutes (range: 50-150 minutes), while the NSM operations lasted for 76 minutes (range: 43-120 minutes) on average.

In total, the overall complication rate was 13.4% (n=18) for ASM and 12.9% (n=12) for NSM. The majority of complications were Grade I, including partial skin/NAC necrosis, seroma, infection or wound dehiscence, which healed spontaneously in both groups.

The median follow-up period was 45.0 months (range: 20.1-82.7). During the follow-up period three distant metastases-related deaths were recorded (ASM:2.2%, n=2; NSM:1.2%, n=1), five local recurrences were observed in preserved areola or the nipple (ASM:3.4%, n=3; NSM:2.4%, n=2), while overall six distant metastatic diseases were recorded (ASM:5.6%, n=5; NSM:1.2%, n=1). There was no significant difference in disease-free survival (p=0.762) and overall survival (p=0.601) between the two groups. The median time until adjuvant treatment initiation was 7.4 weeks (range: 4.6 – 11.9) for ASM and 8.1 weeks (range: 4.1 – 12.0) for the NSM group.

Both groups had the same objective aesthetic outcome as measured by a 5-point Likert scale system (ASM median score: 4.1 (range: 2-5); NSM median score 4.3 (range: 2-5)). The results of the corresponding BREAST-Q domains showed no significant difference between ASM and NSM patients.

4.3. A survey on the needs of Hungarian breast cancer patients regarding modern oncoplastic breast surgery

Understandably, breast loss significantly embarrassed the respondents, with answers averaging 8 ± 3 (mean ± standard deviation (SD)) on a scale of 1 to 10; and there was no difference between the responses in terms of education or marital status.

Based on the answers, 39% (n = 194) of the interviewed women would have been satisfied with breasts resulting in a pretty décolletage in brassiere, however, 28% (n = 140) would have liked to have more beautiful breasts than the original ones were, and 20% (n = 99) wanted perfect breasts at the end of the reconstruction process. In terms of expectations, there

was a significant relationship with education: higher education was associated with higher expectations ($p < 0.05$).

For an optimal aesthetic outcome, 43% (n = 217) of the survey participants would have undertaken a maximum of two and 37% (n = 184) up to three or four operations.

The opinions varied on how funding should be provided: according to 44% (n = 220) of the patients, the health insurance company should cover a maximum of three to four operations, 21% (n = 107) thought that a maximum of two surgeries should be funded, while almost a third of the study population (31%; n = 157) had the opinion that no matter how many interventions were needed, they should all be paid for by the National Health Insurance Fund of Hungary (Nemzeti Egészségbiztosítási Alapkezelő, NEAK). Women with a high school education were less likely to justify more surgeries from state funding, while those with a university degree favoured that ($p < 0.05$). Fifty-five percent of patients (n = 275) believe that age-related changes in reconstructed breasts are an individual aesthetic plastic surgery issue, however, 28% (n = 139) shared the opinion that in the future, even after decades from the primary operation, the management of such problems will belong to the oncologic reconstructive surgery, and would not be an independent aesthetic surgical procedure only.

Patients had a clear view of the surgeon performing the procedure: 90% of them (n = 448) would have entrusted the reconstruction to a plastic surgeon, moreover, 86% (n = 430) said that modern surgical care for breasts cancer should be performed by specially trained breast surgeons, instead of general surgeons, as currently happens. The vast majority of respondents (79%; n = 394) did not consider it acceptable that there are currently only one or two certified breast surgical centres in Hungary.

5. DISCUSSION

5.1. The location of the SLNs in the anatomical axillary subregions: the importance of the careful implementation of the RT or ARM techniques

Nowadays, due to the early detection, the number of early-stage breast cancer requiring treatment is increasing. Around three-quarters of these patients have clinically negative axilla (cN0), in which cases SLNB is performed instead of ALND. SLN has a metastatic involvement in 20-30%. Our SLN positivity rate was 20.2% (n=176). In most of these cases ALND is

omitted and axillary RT is applied. In case of SLN positivity (pN1(sn)), the 4th Hungarian Breast Cancer Consensus Conference recommends the irradiation of all four axillary levels in most cases if the ACOSOG Z0011 criteria are fulfilled and ALND is omitted. Our results show that the coverage of the axillary subvolumes with conventional WBI or thoracic RT fields is not sufficient. Moreover, in some cases due to the rare location of the SLN, even the axillary subregion of SLN was not or wouldn't have been covered by the conventional tangential fields.

There are several studies concerning the coverage of axillary lymph nodes from whole breast tangential field irradiation. Reed et al. reported that using STgFs, no patient received complete coverage of the axillary Level I–II lymph node volumes. Krasin et al. showed that the use of STgFs does not therapeutically treat the regional lymph nodes. Reznik et al. observed that adequate coverage of Level I, defined as 95% of the volume received 95% of the dose, was not achieved in any of the patients using usual tangent fields nor in 6 patients (6 of 35) using high tangents. In a study by Orecchia et al., the Level I nodes were included partially only in the STgF, and the mean dose was only 48.7% of the prescribed dose.

Our results are consistent with the earlier studies that showed that STgFs do not adequately cover the axillary volumes. In summary, adequate coverage of the axilla including the Levels I, II and III should be defined (delineated) based on anatomical structures as all the guidelines suggest; STgFs provide limited coverage of the axilla, and although HTgFs may provide complete coverage of Level I volume in some patients, this is not a rule.

The importance of the irradiation of the SNLB area is yet unknown, however, it seems rational to include that in continuum with the axillary nodal regions in SLN positive cases. In our study, in 9 (1.0%) of the positive SLN cases the affected nodes were related to the apical and 11 (1.3%) of the metastatic lymph node cases were related to the lateral subregions. In total, in 20 patients with positive lymph nodes (2.3% of all cases), the SLNB region would have been left untreated if STgFs were applied to treat the axilla.

In our view, for the proper treatment of the axilla, an additional axillary and supraclavicular RT field is needed. Actually this solution was applied in the Hungarian OTOASOR prospective randomised clinical trial with axillary and supraclavicular field irradiation in the case of a metastatic SLN without ALND.

The subregional localisation of the ARM nodes has not yet been deeply investigated or clearly identified, but it seems obvious that majority of the lymphatics draining the upper limb traverses deep in the axilla. This was also confirmed by Ikeda et al., and Bedrosian et al., who found ARM nodes in zones that correspond the most to the lateral, apical and posterior axillary subregions. Moreover, both studies reported positive ARM nodes only in the lateral and apical subregions, where our results showed the highest SLN positivity rates (22.9% and 30.0%, respectively).

In our study, 280 (32.2%) SLNs were found within one of these subregions, and 22.5% (n=63) of them were positive. This means that 7.2% of all our cases had at least one positive lymph node in the expected ARM lymph node regions. Our results support the scepticism about the oncological safety of the ARM technique; we believe that proper indications, improved patient selection criteria and further investigations are needed for the safe application of the ARM technique.

5.2. Oncological and cosmetic outcome after areola-sparing mastectomy and nipple-sparing mastectomy

In recent years, NSM has become the primary mastectomy technique for prophylactic and therapeutic breast cancer surgical treatment. Several reviews have been published regarding its indications, oncological safety and aesthetic outcomes. Weber et al. reported the recommendations of the Oncoplastic Breast Consortium consensus conference on NSM, which currently provides the highest level of evidence of NSM application.

After the international acceptance of NSM in the field of breast cancer surgery, the implementation of skin-sparing mastectomy (SSM) has declined significantly. Several papers analyse the oncological safety, feasibility and possible indications of SSM in breast cancer surgery, but significantly less similar studies are available for ASM in the international literature. However as reported by Simmons et al., ASM seems to have similar oncological safety, based on the examined 217 mastectomy specimens. The authors reported areola involvement in only 0.9% (n=2) of the cases. Banerjee et al. obtained exactly the same results and found 2 cases of areola involvement out of 219 mastectomy specimens. The present study did not find significant differences in oncological safety between ASM and NSM.

Other studies by Simmons et al. examining 17 patients with ASM and immediate breast reconstruction reported one postoperative complication (localized wound infection) and no locoregional recurrence in the 2-year-long follow-up period with excellent aesthetic outcomes superior to that after SSM. The operation times in our study were almost equal (80 and 76 minutes) for both procedures. Moreover, the majority of the complications were minor (Grade I) for both ASM (n=12; 9.0%) and NSM (n=9; 9.7%), while the reoperation rates (Grade III complications) were only 2.2% (n=3) and 2.1% (n=2) for ASM and NSM, respectively. Regarding the initiation of adjuvant treatment after surgery, Harmeling et al. by reviewing fourteen studies of 5,270 patients found that mean time from mastectomy with immediate breast reconstruction to adjuvant therapy varied between 29 and 61 days. Albright et al. retrospectively analysed 129,951 cases comparing NSM to SSM and reported that NSM was not associated with a delay in delivery of adjuvant chemotherapy or hormonal therapy compared to SSM. In our study, no delay was detected regarding the adjuvant treatment, it was initiated within 12 weeks after surgery in all cases (ASM: median 7.4 weeks (range: 4.6 – 11.9); NSM: median 8.1 weeks (range: 4.1 – 12.0)).

5.3. The needs and attitude of Hungarian breast cancer patients towards modern breast reconstruction

It is clear from the results that breast loss significantly disturbs female patients regardless of education and marital status. These findings correspond to the results of a questionnaire survey of 500 female patients between 2010 and 2011 published by our working group in 2014.

Patients had high expectations for the aesthetic outcome of the operations. Informing patients preoperatively about the realistic outcome is one of the top priorities, because oncoplastic procedures are not aesthetic operations, and albeit due to the technique they are often capable of providing the same high level of result as aesthetic surgeries do, but are completely subordinated to oncological priorities and principles (e.g. resection site, extent, RT, etc.). Given that the structure of the two breasts differs during the most frequently applied implant-based post-mastectomy reconstructions, breast asymmetry increases over time. Based on this, later on patients have secondary surgical demands due to the changes in symmetry over time.

According to the surveyed women, the desired high cosmetic result was wanted to be achieved by two, or not more, than three or four operations at maximum, which, in their view, should be covered by the NEAK. At present, the system is able to provide oncoplastic surgery capacity to an artificially limited number of cases and probably only with a limited number of elements of the field. It is a question, how could a full oncoplastic breast surgery capacity be ensured to all.

Patients would entrust specially trained breast surgeons practising in oncoplastic breast surgery centres with their surgical treatment, because, in their opinion, this would have a significant impact on their recovery. The need for oncoplastic breast reconstruction following mastectomy in Hungary is in line with international trends: according to a British study, 50% of female patients awaiting breast removal, while according to a French study by Ananian et al., 81% of such patients would like to have breast reconstruction. Understanding the needs of the affected women, providing adequate information and adequate access to surgical care, organizing patient routes and properly structuring the health care system is essential for the expansion of oncoplastic breast cancer care.

6. CONCLUSIONS

6.1. No significant relationship exists between the location or histopathological parameters of the primary breast tumour and the subregional localisation of the SLN; the majority of SLNs are located in the anterior and central anatomical subregions of the axilla.

6.2. In the era of conformal radiotherapy, instead of schematic solutions, individualised radiotherapy planning according to the risk status is needed to ensure the adequate coverage of axillary nodal volumes.

6.3. Further investigations and caution are needed for the use of the ARM technique during ALND; our results should draw attention to that the practice of the ALND plus ARM technique involves the risk of leaving behind metastatic lymph nodes in the apical, lateral or posterior axillary subregions in a significant proportion of cases resulting in

understaging and undertreatment. The application of SLNB during the intervention of ARM + ALND in a selected group of cases should be investigated.

6.4. ASM and NSM are equivalent alternatives providing similar complication rates, oncological safety aesthetic outcome and patient satisfaction in adequately selected cases; our results indicate that preserving the natural pigmented skin envelope of the areola has the same importance as the conservation of the complex NAC itself. ASM could be a suitable treatment option if NSM is not oncologically feasible.

6.5. State-of-the-art surgeries performed by qualified breast surgeons in dedicated centres providing physical and psychological recovery is needed and required by a significant proportion of Hungarian breast cancer patients.

7. ACKNOWLEDGEMENTS

I would like to thank:

- Dr. med. habil. Zoltán Mátrai for his time, continuous support, scientific guidance and professional supervision of my thesis

- Dr. Dávid Pukancsik, Dr. Tamás Mátrai and Dr. Mihály Újhelyi for their continuous support as core members of the oncoplastic clinical scientific team and editing, preparing some of the related articles

- Prof. Dr. Miklós Kásler former Director and Prof. Dr. Csaba Polgár Director of the NIO for providing me with the professional environment and facilities of the National Institute of Oncology to complete the thesis

- Prof. Dr. Mihály Bak for the guidance in the scientific doctorial school

- my colleagues and co-workers of the National Institute of Oncology, especially in the Breast and Sarcoma Surgery Department for assisting in data collection

- Bence Bukovszky, Prof. Dr. János Fodor, Prof. Dr. Csaba Polgár and the Centre of Radiotherapy for providing data and assisting in radiotherapy CT simulations

- Radiological Diagnostics for providing data for the studies

- the Department of Surgical and Molecular Pathology for providing data used in this study

- Dr. István Kenessey for his professional assistance with the statistical analysis

- Dr. Ágnes Nemeskéri for providing me all the support and facilities for the cadaveric dissections in the Department of Human Morphology and Developmental Biology, Semmelweis University

- my family for their understanding and support during the completion of this thesis