# TO THE QUESTION OF THE RISK OF POSTMATECTOMY LYMPHEDEMA IN PATIENTS WITH BREAST CANCER AND ITS CONNECTION WITH CONCOMITANT VASCULAR PATHOLOGY

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***Abstract.*** *Investigation resultsof influence of radical mastectomy (RME) combined with lymphatic-venous anastomosis (RME+LVA) to the 5-year survival of patients with breast cancer (BC), to current of BC, and to the risk of development secondary postmastectomy lymphedema (VL), and to its link with symptoms of atherosclerosis, ischemic illness of heart, coronary sclerosis, stenocardia, vascular diseases of the brain, neurocirculatory dystonia and hypertensive disease (HD) are presented. It is shown that RME+LVA effectively reduces risk of SL at patients with BC, not influencing current breast cancer, their 5-year-old survival, and that, probably, risk of VL is linked to the factors which prevent development of HD.*

***Keywords:*** *radical mastectomy, anastomosis, breast cancer, lymphedema.*

**Introduction:** The effectiveness of cancer treatment is determined not only by its course, but largely by concomitant vascular pathology (CVP) [29; 30], which largely determines the material and labor costs of surgical treatment [27]. Excision of the tumor within healthy tissue is an important component of complex and combined treatment of cancer. The tactics of adjuvant and neoadjuvant polychemotherapy (PCT) and radiation treatment (RT) have made it possible to expand the indications for radical mastectomy (RM) for almost all stages of locally advanced breast cancer (BC) [31]. RME is associated with a risk of serious complications, in particular secondary lymphedema (SL) [7; 8;16]. The problem of VL is becoming especially significant in connection with the development of practices for early diagnosis of breast cancer, which contributes to an increase in the number of patients with indications for RME and, accordingly, their life expectancy, bringing to the fore issues of quality of life [6;7;8], which largely determines the overall viability of treated patients and the outcome of the disease.

Treatment and prevention of VL are associated with additional burdens on medical institutions and the need for periodic medical monitoring of the condition of operated patients. In this regard, surgical prevention by applying lymph venous anastomosis (LVA) on the side of the operation is considered as a promising direction in modern oncological practice. Thus, in 2021, a blind randomized study of the effectiveness of LVA was launched at the Ghent University Hospital (USA).in the prevention of VL associated with surgical treatment of breast cancer, involving 80

patients. [eleven]. By us in 2017-2022 We conducted a study of the effectiveness of simultaneous application of LVA with RME (RME+LVA) in the prevention of postmastectomy VL.

Purpose of study: Assessment of the effect of RME+LVA on the course of breast cancer, five-year survival of patients, the risk of developing VL in them and its relationship with signs of CVS detected before surgery - coronary heart disease (IHD), atherosclerosis (AS), coronary-cardiosclerosis (CC), angina (rest and stress) (SC), hypertension that has reached stage IIb (stage IIb hypertension), cerebral atherosclerosis (ACVM) and neurocirculatory dystonia (NCD).

**Materials and methods.** The study sample was formed from a population of patients with stage II breast cancer. groups, first identified in the Samarkand region for the period 2017-2020, the treatment of which included RME for various clinical indications -in accordance with the concepts of primary inoperable (locally advanced) and primary operable cancer.

The total population of this (general) population was 1078 cases of breast cancer. The sample consisted of the following main groups of patients: group I, compiled prospectively – 70 patients with stage I-IIIA breast cancer who underwent surgery RME+LVA; II – control group of 120 patients, compiled retrospectively by random selection from a total of 1078 patients treated with RME (without LVA). Group II was divided into two subgroups: IIa - main control (92 patients with stage I-IIIA breast cancer, that is76.67% of patients in group II), statistically similar to I; IIb – indirect control (the remaining 28 patients with stages IIIB-IIIC-IV breast cancer, secondary, metachronous breast cancer (23.33%group II). *LVA application method* described in our previous work [33]. Current clinical standards were used [31].

Patients, as a rule, received 4-6 courses of preoperative PCT, postoperative PCT and LL (in the standard radiation dose fractionation mode) taking into account the stage of the process. In stage IV locally advanced breast cancer, patients were offered palliative chemotherapy or chemoradiotherapy and simple sanitary mastectomy. For LL, remote telegammatherapy was used (installations: SIMVIEW NT from the German company Siemens, THERATRON - 780E from the Canadian company MDS - nordion), calculating topometric maps based on data from X-ray simulation, P-X-ray, computed tomography (CT, MRI), endoscopic and sonographic (ultrasound) studies.

The control period of the study was from 01/01/2017 to 07/01/2022. After completion of special treatment, patients were given standard recommendations for appearing for control. The timeliness of their appearance for control was recorded.

Observation was considered completely terminated in the event of the death of the patient or her complete withdrawal from direct observation (due to her leaving the region or republic). The observation results extracted from inpatient and outpatient records were transferred to an electronic codifier and subjected to statistical analysis on a computer in accordance with generally accepted principles of statistics [14;18;20;26;28;32].

**Research results and discussion**

During observation (Table 1), no cases of VL were detected in group I by the control date;in group II, VL developed in 18 patients (16 in IIa and 2 in IIb). Of the 190 patients in the sample, 22 died: in group II - 15 out of 120 (12.5%); of which 11 out of 92 are in subgroup IIa (12.0%), 4 out of 28 are in IIb (14.29%) ($p>0.05$), 7 out of 70 are in group I (10.0% ). Intergroup differences in the proportion of deaths were not statistically significant ($p>0.05$).

*Table 1*

**Proportional average cases of VL and failure of patients to appear for control during the control period (% of the number of patients in the group)**

| Group | number of observations | VL occurred (%) | cases without VL | did not show up for control |
|---|---|---|---|---|
| I | 70 | 0 (0.00%) | 59 (84.29%) | 11 (15.71%) |
| IIa | 92 | 16 (17.39%) | 56 (60.87%) | 20 (21.74%) |
| IIb | 28 | 2 (7.14%) | 22 (78.57%) | 4 (14.29%) |
| II | 120 | 18 (15.00%) | 78 (65.00%) | 24 (20.00%) |
| Total | 190 | 18 (9.47%) | 137 (72.11%) | 35 (18.42%) |

*Table 2*

**Average observation period of patients during the control period (months) in groups**

| Group (N patients | group as a whole | before signs of VL appear | cases without VL | did not show up for control | without overhead line + those who did not show up for control |
|---|---|---|---|---|---|
| I (70) | | - | 30.12 | 29.87 | 30.08 |
| IIa (92) | | 28.00 | 24.18 | 40.07 | 28.36 |
| IIb (28) | | 27.29 | 20.31 | 29.87 | 21.78 |
| II (120) | | 27.92 | 23.09 | 38.37 | 26.69 |
| Total (N=190) | | 27.92 | 26.12 | 35.70 | 28.07 |
| Confidence intervals (CI95%) for mean follow-up periods | | | | | |
| Groups (N) | Average follow-up time for patients (months) | | | | |
| | group as a whole | before signs of VL appear | no swelling | those who did not show up for control | without overhead line + those who did not show up for control |
| I (N=70) | 28.71÷31.29 | - | 28.83÷31.41 | 28.58÷31.16 | 28.79÷31.37 |
| IIa (N=92) | 27.34÷29.26 | 27.03÷28.97 | 23.26÷25.10 | 39.02÷41.12 | 27.39÷29.33 |
| IIb (N=28) | 19.10÷25.30 | 23.97÷30.61 | 17.31÷23.31 | 26.46÷33.28 | 18.70÷24.86 |
| II (N=120) | 26.17÷27.63 | 27.18÷28.66 | 22.40÷23.78 | 37.57÷39.17 | 25.96÷27.42 |
| Total (N=190) | 28.03÷28.97 | 27.45÷28.39 | 25.67÷26.57 | 35.20÷36.20 | 27.61÷28.53 |

The average follow-up period (Table 2) was 30.0 in group I, 28.3 in subgroup IIa (the difference is not statistically significant - $p>0.05$); while in group II it was 26.9 months, in subgroup IIb – 22.18 (the difference with group I is statistically significant - $p<0.05$). The average follow-up periods for patients before the onset of edema and without it in group II (and subgroups IIa and IIb) differed statistically significantly ($p<0.05$), in contrast to intergroup differences ($p>0.05$). At the same time, the average follow-up period for patients who had no signs of VL

during the control period in group I was statistically significantly ($p<0.05$) different from that in group II (including in subgroups IIa and IIb), and between subgroups IIa and IIb this difference was borderline significant ($0.1>p>0.05$).

In some patients who did not show up for follow-up, At their place of residence, there are no observations of signs of VL occurring in them. They were included in the group of patients "without VL + those who did not show up for control" (which we considered necessary to clarify judgments about the real difference between the groups). The average follow-up period in this population of patients was statistically significantly shorter in subgroup IIb than in IIa and group I ($p<0.05$).

The cumulative probability of 5-year survival after RME (Table 3) for the entire sample was 88.4%; while in group I - 90.0%, in group II - 87.4 (subgroup IIa - 88.0, subgroup IIb - 85.2). Intergroup differences in all comparison pairs were not statistically significant for any pairwise comparisons ($p>0.05$). That is, the probability of five-year survival was not significantly affected by RME+LVA compared with conventional Madden RME.

***Table 3***

| Group of patients | Number of patients | Cumulative probability of 5-year survival after RME, % | CI95,% |
|---|---|---|---|
| Entire sample | 190 | 88.4 | 83.7÷93.0 |
| Group I | 120 | 90.0 | 82.8÷97.2 |
| Subgroup IIa | 92 | 88.0 | 81.4÷94.7 |
| Subgroup IIb | 28 | 85.2 | 71.0÷99.4 |
| Group II | 70 | 87.4 | 81.3÷93.5 |

At each presentation, patients were examined, recording facts of recurrence of the underlying disease (metastasis to distant organs - bones, lungs, liver, dissemination on the surgical scar), the development of complications associated with treatment and reducing the quality of life of patients, in particular VL, and manifestations of SP.

Table 4 shows the distribution in groups of the fractional average parameters we studied - the frequencies of 1) metastasis to distant organs, 2) signs of VL, 3) absence of complications and 4) failure of patients to appear for control after special treatment (in%) and their 95% confidence intervals at the time of their last follow-up appearance.

The proportion of cases of distant metastasis in subgroup IIb statistically insignificantly prevailed over that in group I and subgroup IIa ($p>0.05$), which was expected, given that in subgroup IIb (25, 0% of cases) were all patients with stage IIIa of locally advanced breast cancer. At the same time, groups I and subgroup IIa were almost similar in this indicator - 10.0% and 9.8%.

There were no statistically significant differences between the groups in the proportion of patients who showed no signs of complications when presenting for a follow-up examination ($p>0.05$), and the proportion of patients who did not appear for a follow-up examination ($p>0.05$).

Significant intergroup differences were noted for the frequency of appearance of signs of VL during the control period: in patients of group I, where not a single case of VL was detected, the probability of this event was significantly less than in group II ($p<0.05$) and subgroup IIa ($p<0.05$ ), not significantly less than in IIb ($p>0.05$).

*Table 4*

**Distribution of clinically significant conditions identified when patients showed up for follow-up examination, %(signs of SP are given in Tables 5a and 5b)**

| Signs | Group I (n=70) | | Subgroup IIa (N=92) | | Subgroup IIb (N=28) | |
|---|---|---|---|---|---|---|
| | Number of cases | M+m,% | Number of cases | M+m,% | Number of cases | M+m,% |
| Metastasis to distant organs | 7 | 10.0+3.6 | 9 | 9.8+3.1 | 7 | 25.0+8.2 |
| No complications or relapses | 40 | 57.1+5.9 | 44 | 47.8+5.2 | eleven | 39.3+9.2 |
| Signs of VL | 0 | 1.4+1.4 | 16 | 17.4+4.0 | 2 | 7.1+4.9 |
| Didn't show up after special treatment | eleven | 15.7+4.4 | 20 | 21.7+4.3 | 4 | 14.3+6.6 |
| 95% confidence intervals of fractional means, CI95,% | | | | | | |
| Metastasis to distant organs | 2.97÷17.03 | | 3.71÷15.85 | | 8.96÷41.04 | |
| No complications or relapses | 45.55÷68.74 | | 37.62÷58.03 | | 21.20÷57.38 | |
| Signs of VL | 0.00÷5.37 | | 9.65÷25.14 | | 0.00÷19.08 | |
| Didn't show up after special treatment | 7.19÷24.24 | | 13.31÷30.17 | | 1.32÷27.25 | |

Table 5 givesdistribution in groups of patients according to the characteristics of seven nosological units of the SSP at their last appearance during the control observation period. In the lower half of the table are the same data recalculated to the structure of the distribution of signs of these seven nosologies in group II. That is, group II is taken in these recalculations as the "standard" against which intergroup comparisons are made. There were no statistically significant differences between the study groups (I, II, IIa and IIb) ($p>0.05$), including according to the data recalculated to the "standard". These results do not allow us to state that the risk of VL after RME is directly linked (or not linked) with SSP in patients with breast cancer, as a number of authors believe [3;10;12;15;19;21;23;24]. Apparently, the relationship between CSP and the risk of VL developing after RME are determined by the degree of involvement of the SSP and lymphatic systems in the compensatory reactions of the body after RME. To complete the picture of the relationship between SSP and the risk of VL after RME, further research is needed.

We believe that the body of patients in group IIb more effectively realized the compensatory abilities of the lymphatic drainage system on the side of the operation than in IIa. On the other hand, it seems that in the body of patients in group I, the LVA is involved in restoring the level of lymphatic drainage in the area of lymphatic structures removed during RME on the side of the operation, which allows interstitial fluid to directly enter the venous system, which reduces the risk of VL even in the presence of SSP. In group II patients, the body strives to independently restore the drainage function damaged during surgery. At the same time, the risk of VL in subgroup IIb was at least no higher than in IIa.

*Table 5*

**Fractional averages of ERP signs occurring in patients of the compared groups (M,%) and their confidence intervals (CI95%)**

| SSP | I | | IIa | | IIb | | II | | Entire sample | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number b-x | M,% | Number b-x | M,% | Number b-x | M,% | Number b-x | M,% | Number b-x | M,% |
| IHD | 37 | 52.86 | 36 | 39.13 | 17 | 60.71 | 53 | 44.17 | 90 | 47.37 |
| AC | 35 | 50.00 | 33 | 35.87 | 16 | 57.14 | 49 | 40.83 | 84 | 44.21 |
| KKS | 34 | 48.57 | 33 | 35.87 | 16 | 57.14 | 49 | 40.83 | 83 | 43.68 |
| SK | 2 | 2.86 | 3 | 3.26 | 1 | 3.57 | 4 | 3.33 | 6 | 3.16 |
| GB IIb Art. | 24 | 34.29 | 24 | 26.09 | 13 | 46.43 | 37 | 30.83 | 61 | 32.11 |
| ASGM | 4 | 5.71 | 3 | 3.26 | 3 | 10.71 | 6 | 5.00 | 10 | 5.26 |
| NDC | 32 | 45.71 | 44 | 47.83 | 10 | 35.71 | 54 | 45.00 | 86 | 45.26 |
| SSP | Confidence intervals (CI95%) | | | | | | | | | |
| IHD | 41.16÷64.55 | | 29.16÷49.10 | | 42.62÷78.80 | | 35.28÷53.05 | | 40.27÷54.47 | |
| AC | 38.29÷61.71 | | 26.07÷45.67 | | 38.81÷75.47 | | 32.04÷49.63 | | 37.15÷51.27 | |
| KKS | 36.86÷60.28 | | 26.07÷45.67 | | 38.81÷75.47 | | 32.04÷49.63 | | 36.63÷50.74 | |
| SK | 0.00÷7.81 | | 0.00÷7.26 | | 0.00÷13.75 | | 0.12÷6.55 | | 0.67÷5.64 | |
| GB IIb Art. | 23.17÷45.41 | | 17.11÷35.06 | | 27.96÷64.90 | | 22.57÷39.10 | | 25.47÷38.74 | |
| ASGM | 0.28÷11.15 | | 0.00÷7.26 | | 0.00÷22.91 | | 1.10÷8.90 | | 2.09÷8.44 | |
| NDC | 34.04÷57.38 | | 37.62÷58.03 | | 17.97÷53.46 | | 36.10÷53.90 | | 38.19÷52.34 | |

Fractional averages of ERP characteristics in groups when recalculated to the “standard”(group II); in brackets of the first column - the specific gravity of the “standard” in relative units (RU)

| SSP(O.E. in "standard") | Group I (N=70) | Group IIa (N=92) | Group IIb (N=28) | Group II (N=120) | Entire sample (N=190) |
|---|---|---|---|---|---|
| IHD (0.442) | 23.3 | 17.3 | 26.8 | 19.5 | 20.9 |
| AC (0.408) | 20.4 | 14.6 | 23.3 | 16.7 | 18 |
| KKS (0.408) | 19.8 | 14.6 | 23.3 | 16.7 | 17.8 |
| SK (0.033) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| GB IIb Art. (0.308) | 10.6 | 8 | 14.3 | 9.5 | 9.9 |
| ASGM (0.050) | 0.3 | 0.2 | 0.5 | 0.2 | 0.3 |
| NDC (0.450) | 20.6 | 21.5 | 16.1 | 20.2 | 20.4 |
| SSP(OE) | Confidence intervals (CI95%) | | | | |
| IHD (0.442) | 13.44÷33.26 | 9.56÷25.01 | 10.41÷43.22 | 15.14÷26.70 | 12.42÷26.60 |
| AC (0.408) | 10.97÷29.86 | 7.42÷21.87 | 7.67÷39.00 | 12.58÷23.52 | 10.00÷23.34 |
| KKS (0.408) | 10.49÷29.17 | 7.42÷21.87 | 7.67÷39.00 | 12.39÷23.28 | 10.00÷23.34 |

| | | | | | |
|---|---|---|---|---|---|
| SK (0.033) | 0.00÷1.45 | 0.00÷1.35 | 0.00÷2.55 | 0.00÷0.92 | 0.00÷1.19 |
| GB IIb Art. (0.308) | 3.37÷17.77 | 2.49÷13.60 | 1.34÷27.29 | 5.65÷14.15 | 4.26÷14.75 |
| ASGM (0.050) | 0.00÷2.50 | 0.00÷1.65 | 0.00÷5.41 | 0.00÷1.46 | 0.00÷1.79 |
| NDC (0.450) | 11.10÷30.04 | 13.12÷29.92 | 2.47÷29.68 | 14.64÷26.10 | 13.06÷27.44 |

Theoretically, the influence of chance on the composition of the formed groups is acceptable, but in our case its probability is negligible, since the number of patients in groups I and II is quite large. Functional and structural restoration of lymphatic drainage function after RME depends on the compensatory capabilities of the body, which are only partially related to chronological age. the nature of this connection is individual, and it is impossible to foresee it in advance. The body's ability to compensate for an anatomical disorder in the drainage function of the lymphatic vasculature can be influenced by various factors; the nature of the influence of SSP on long-term results of RME is also individual. Attention to SSP is important due to the fact that there is reason to associate with them the risk of involvement of the lymphatic system in the pathogenesis of VL [19]. SSP is largely associated with cholesterol metabolism disorders, associated with the state of lymphatic vasculature [3;10;15; 24], which is manifested by the occurrence of lymphatic edema after surgical interventions [10; 12; 21; 23].

As independent risk factors for VL in patients with breast cancer, surgical excision of lymph nodes, radiation and chemotherapy as part of the strategy ***radical treatment of breast cancer*** [2; 5; 6; 7; 9; 10; 22], and the total risk of VL is determined by the imposition of risks from each of these three methods [1; 25]. Our data are close to the data of the authors who showed that VL occurs after treatment of breast cancer in 15-20% of cases [4; 13], although depending on the level of diagnosis, its frequency can vary widely – from 5 to 50% [5; 17; 22]. In general, there is no doubt that the risk of developing VL after RME is largely individual and is determined by genetic factors and the characteristics of the patient's anatomy, which are still poorly studied and poorly understood [7]. These features are realized during the individual life of the patient as elements of his phenotype (constituting the morphological and physiological characteristics of the organism).

Whatever the mechanisms that realize the risk of VL in patients with breast cancer after RME, the results obtained are quite consistent with the idea of using the operation of RME + LVA to prevent VL and preserve the quality of life of patients in this category. Taking them into account seems important for planning and coordinating the activities of cancer-mammalogical and lymphological services. The randomized nature of the study allows us to predict the most likely effect of the use of RME+LVA surgery on a population scale. The freed up medical time and funds can be used to further improve oncological services in the region.

Thus, at this stage of the study, the following conclusions, which have clinical and organizational significance, can be drawn.

**Conclusions:**

1. Operation according to the "RME+LVA" scheme 10-fold (compared to traditional RME according to Madden, without LVA), reduces the likelihood (risk) of developing signs of VL in patients with breast cancer, at least during the five years of the postoperative period.

2. There were no statistically significant differences between the operations "RME+LVA" and "RME without LVA" in their impact on the course of the main process, the probability of five-

year survival and its connection with concomitant vascular pathology in patients with breast cancer.

3. It is assumed that the widespread use of RME+LVA surgery will provide significant changes in the quality of life of patients with breast cancer at the population level; The freed up medical time and funds can be used to further improve oncological and lymphological services in the region served by a specialized oncological institution.

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