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STUDY OF THE EFFECTIVENESS OF IMPOSITION OF LYMPHATIC-VENOUS ANASTOMOSIS FOR THE PREVENTION OF SECONDARY LYMPHEDEMA AFTER RADICAL TREATMENT PATIENTS WITH BREAST CANCER (PRELIMINARY RESULTS)

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Abstract

Prevention of secondary lymphedema (LL) after radical treatment of breast cancer (BC) is an urgent task of modern oncology. Description of preliminary results of a study of the effect of radical mastectomy (RME) with lymphatic-venous anastomosis (LVA) on the frequency of VL, 5-year survival of patients and the risk of VL, conducted in the Samarkand region . And out of 1078 registered for the first time in 2017-2020. patients with breast cancer, subjected to RME according to clinical indications, made up a sample of 190 patients, dividing it into three groups. Group I consisted of 70 patients with I - IIIA stages of breast cancer, subjected to RME according to Madden with simultaneous application of LVA; group II - 120 patients randomly selected from the remaining 1008 patients subjected to RME without LVA. Subgroup II and group II included 92 patients with stage I - IIIA breast cancer (76.67%) ; in subgroup II b - the remaining 28 with stages IIIB , IIIC and IV , metachronous breast cancer (23.33%) . During the study period, 22 patients died (11.58%): in group II - 15 (12.50%), 11 of them - in subgroup IIa (11.96%), 4 - in II b (14.29%) ;, differences are not significant ($p > 0.05$). The mean follow-up period in the sample was 28.5 months: in group II - 26.9, in subgroup IIa - 28.3, in subgroup IIb - 22.18; in group I - 30.0. The distribution of patients in groups I and II by stages was statistically similar ($p > 0.05$). RME with LVA had no effect ($p > 0.05$) on the dynamics of the five-year survival of patients compared with conventional RME. RME with LVA reduced the risk of VL ($p < 0.05$) in patients with breast cancer for 5 years, which did not depend on the stage of breast cancer. The results indicate the high efficiency of LVA in patients of the II clinical group, falling under the indications for the use of RME .

Keywords: breast cancer, radical mastectomy, lympho-venous anastomosis , secondary lymphedema ..

RELEVANCE

The problem of early initiation of treatment and prevention of *secondary lymphedema* (VL) is especially relevant due to the prolongation of remission periods, improvement of long-term results of treatment . patients with breast cancer (BC) and , accordingly, an increase in the number of patients surviving after treatment [1, 2, 3, 4]. The increase in VL is associated mainly

with *radical mastectomy* (RME) and the inevitable removal of the axillary lymph nodes [5], which becomes the main risk factor for the development of VL . In modern Uzbekistan, serious attention is paid to early detection and early treatment of breast cancer, the problem of VL is especially relevant. In order to reduce the likelihood of developing VL in the immediate and long-term periods of radical treatment of breast cancer in the Samarkand branch of the Republican Scientific and Practical Center Since 1917, the MZRUz has introduced into practice the combined Madden RME operation with simultaneous imposition of *lymphatic-venous anastomoses* (LVA) on the side of the operation, the effectiveness of which has been emphasized by many authors in recent years [6, 7, 8, 9]. In this regard, studies are being conducted to identify *risk factors* and *predict* the occurrence of VL after RME and its *course* in conjunction with the likelihood of survival and quality of life of patients, which is important from the point of view of developing the practice of effective prevention of VL after special treatment for breast cancer. The purpose of this report is to describe the features of this study and to preliminarily evaluate the effectiveness of RME with LVA overlay compared to the use of RME alone in terms of survival dynamics and VL development.

MATERIALS AND METHODS

Main principles of research . And the study is planned in such a way as to project the properties *of the general population onto the study sample* - all patients diagnosed with breast cancer, registered for the first time and subject to radical treatment and taken into account by the annual reports of the regional branch of the RSMC O &R in 2017-2020. The results obtained in this way will make it possible to achieve the main goal of the study - to evaluate the effectiveness of the use of RME with the simultaneous application of LVA on a regional scale.

study planning . It is assumed that the study sample should represent the totality of patients with breast cancer II cl . gr., subjected to RME for various clinical indications for RME (1078 cases of RME for the period 2017-2020). The study groups should be formed in such a way that the results of the study will improve the predictive planning of the clinical activities of the branches of the RMNCROiR MZRUz based on a quantitative assessment of the effectiveness of RME with simultaneous application of LVA using clinical standards for the treatment, screening and prevention of breast cancer.

Research groups . In accordance with the indications for RME, a sample of patients was randomly selected, from which the following study groups were formed:

group I - 70 patients with stage I - IIIA breast cancer, subjected to RME according to Madden with simultaneous application of LVA - the main study group;

group II - the control group was composed by random selection of 120 patients from a total of 1078 patients of clinical group II , subjected to RME for various indications (without LVA) during 2017-2020. This group, in turn, was divided into two subgroups:

subgroup IIa - the main control, which included 92 patients with stage I - IIIA breast cancer (76.67% of the entire control group II) , subjected only to RME, which from a clinical point of view did not statistically differ from the main group, group III ;

subgroup II b - additional control, which included 28 patients with stage III B , III C and IV stages of breast cancer and with secondary, metachronous breast cancer that arose after the

treatment of primary cancer (these patients are included here to exclude the influence of previous medical interventions on the body of a patient with breast cancer), subjected only to RME and amounted to 23.33% of the control group.

Thus , all groups were formed based on clinical considerations regarding the expediency of radical surgical treatment of breast cancer - RME with and without LVA. Therefore, the studied sample as a whole statistically reflects the entire population of patients with breast cancer, first identified and registered in the Samarkand region, in the stages of the disease that fall under the strategy of radical treatment, including RME. Therefore, a comparative analysis will allow us to analyze at the population level the contribution of RME to the final effect of interventions for breast cancer in patients of the II clinical group. This effect obviously depends on the therapeutic, anesthetic risks, the condition of patients after surgical treatment, comorbidity, which can, in particular, affect the level of lymphatic drainage function of the tissues affected during treatment, the adequacy of the application of clinical standards, etc. Considering these factors, we expect to obtain statistically sound conclusions and conclusions that will influence the long-term planning of the clinical activities of the regional oncological service.

LVA overlay carried out immediately *upon completion of the* RME according to Madden . Subcutaneously, in the axillary region on the side of the operation, 2 cm away from the axillary line, a 2% solution of methylene blue was injected, a 5-10 minute massage is performed. 10 minutes after the injection of the solution, when methylene blue begins to be released from the lymphatic vessels, a lymphatic vessel was found using a microscope with a 30-40x magnifier and connected with polyamide threads 10.0 using the “end-to-end” or “end-to-side” method. ” with one of the thoracodorsal veins. The tightness of the anastomosis was verified within 10 minutes of observation, noting the clarification of the lymphatic fluid flowing into the vein.

Compliance with clinical standards during the study . In the process of managing patients, clinical standards approved by the Ministry of Health of the Republic of Uzbekistan on the basis of the Decree of the President of the Republic of Uzbekistan No. 2866 of 4.04.17 were used. Approved by the Order of the Ministry of Health of the Republic of Uzbekistan No. 351 dated 2017.29.06. **[10]** , in accordance with which anamnesis was taken, examination of patients, laboratory tests (general blood count, biochemical blood test, bilateral mammography, ultrasound of the mammary glands and regional zones, MRI, mammary glands, MRI and ultrasound of the chest, abdominal cavity and small pelvis , radioisotope examination of the skeleton + X-ray and / or CT / MRI of the areas of accumulation of the radiopharmaceutical (*if indicated*), R-graphy of the chest organs , biopsy of the tumor with pathomorphological examination of the tumor tissue Estrogen receptors (ER) and progesterone were determined in the tumor tissue (RP), HER2 and Ki67, evaluated ovarian function.Pathological examination of *the removed tumor tissue* determined *:* a) histological variant of the tumor; b) degree of differentiation; c) condition of resection margins; d) severity of lymphovascular invasion; e) condition of axillary lymph nodes; f) content of RE, RP, HER2 and Ki67 by IHC method; g) the severity of the pathomorphological response in the primary tumor and regional lymph nodes (in the case of preoperative drug therapy), taking into account the possible heterogeneity of the tumor. When planning surgical interventions, we took into account the standard concepts of primary operable and locally advanced (primarily inoperable) breast cancer, which determine the place and role of surgical strategy in the treatment of breast cancer.

Patients, as a rule, received ***4-6 courses of preoperative polychemotherapy*** (PCT) and postoperative PCT and radiation treatment in the mode of standard fractionation of the radiation dose, taking into account the stage of the process, in accordance with standard algorithms for the treatment of patients with breast cancer. All patients who have gone to Stage IV offered palliative chemotherapy or chemoradiotherapy, if necessary - sanitary simple mastectomy.

In ***radiation treatment of*** breast cancer, remote telegammatherapy (DTGT) was used on SIMVIEW units. NT of the German company " Siemens ", " THERATRON - 780E" of the Canadian company " MDS - nordion ". The topometric map displays information obtained during X-ray simulation, as well as data from other research methods (P -X-ray , CT, MRI, EGDFS, ultrasound, histology). Then the radiologist, together with the physicist, carried out the planning of radiation treatment.

Possible contraindications considered ***for surgical treatment*** : cardiovascular and respiratory insufficiency II degree and above; an active form of tuberculosis of the lungs and other organs; serious circulatory disorders, renal and hepatic insufficiency, mental disorders, exacerbations of surgical diseases; and documented refusal of the patient from the proposed treatment options.

The main ***contraindication to chemotherapy*** or an indication for its temporary or complete cessation were reduced hematological and immunological parameters.

The main contraindications to radiation treatment were: 1) tumor decay with bleeding; 2) active form of pulmonary tuberculosis; 3) anemia (Hb less than 80g/l); 4) leukopenia (leukocytes less than 2.0x109/l); 5) thrombocytopenia (less than 75x109/l); 6) myocardial infarction or stroke (by decision of the council); 7) mental disorders during the period of exacerbation; 8) intractable condition of the patient according to the Karnovsky scale of 40% or less.

Observation, timing and scope of examination of patients with breast cancer : After treatment, the patient was invited for a follow-up examination and examination every three months during the first year and every 6 months thereafter until the control date (07/01/2022). If necessary, they were hospitalized, additionally examined. The timeliness of the patient's appearance for a follow-up examination or her absence was recorded. The end result of the study was evaluated based on the results of a three-stage work: 1) diagnostic measures, 2) adequate planning of therapeutic measures, and 3) making additional decisions already in the course of treatment and monitoring the patient. The obtained material is analyzed retrospectively, and the results of the analysis will allow us to study not only clinical, but also organizational factors that can affect the overall outcome of treatment at any of the three stages of patient management. During the study period, only 22 patients died (11.58% of the entire sample). In control group II , 15 patients out of 120 (12.50%) died, of which 11 died in subgroup IIa (11.96% of the subgroup), 4 in subgroup IIb (14.29%). Group differences are not statistically significant ($p > 0.05$).

The average follow-up period for the study sample as a whole was 28.5 months: in control group II it was 26.9 months, in subgroup IIa - 28.3, in subgroup IIb - 22.18, in group I - 30.0. When interpreting data on turnout, one should obviously proceed from the fact that it is largely related to the patient's motivations. On the one hand, patients may feel the need to appear, associated with their feelings of their state of health. On the other hand , this motivation is

determined by the willingness of the patient to follow the recommendations of the attending physician. This willingness obviously depends on her inherent sense of responsibility for her health, and the real ability to follow medical recommendations. At the same time, we believed that in the event of the death of the patient or for another reason, she completely leaves the sphere of medical supervision (for example, leaving the region or republic), the latter is completely terminated.

Selection of the control date of the study . The milestone date was July 1, 2022. When choosing this date, we assumed that the data that would be obtained by this period would allow us to analyze the results of the intervention, taking into account two indicators that are most important for oncological practice - 1) 5-year cumulative survival of patients with breast cancer and 2) the accumulation of complications due to interventions (in the first turn we were interested in VL).

Statistical processing of results . The results of the observation were recorded in the inpatient card (case history) and outpatient card, from where they were transferred to a special electronic codifier, which was then subjected to statistical analysis using a package of standard computer programs. Quantitative processing of the study data was carried out in accordance with generally accepted principles of statistics **[11, 12, 13]** . When obtaining zero and 100% shared averages, tables were used for express calculations of the standard error and confidence limits [**14]** ; group differences were judged by Student's t -test **[15, 16]** .

PRELIMINARY RESULTS OF THE STUDY AND THEIR DISCUSSION

Adequacy of planning to the objectives of the study . The main criterion for the adequacy of the groups made up for the purposes of the study is the statistical similarity of the distribution of patients with shared averages in the study groups depending on the stage of the tumor process in groups I and subgroup IIa of the control group. A parallel comparison of such a distribution in groups I and IIb will allow us to answer the question of whether the occurrence of VL after radical treatment is associated with an oncological diagnosis and associated factors. As shown by the preliminary analysis (see Table 1), groups I and subgroups II b are statistically identical (p >0.05 at all stages of the tumor process). This fact makes it possible to state with a high probability that the groups are formed in accordance with the actual practice of applying the RME, which has developed in the regional branch of the RMSPTSOiR MZRUz and, therefore, a comparative analysis will allow solving problems in accordance with the stated objectives of the study.

Table 1

Distribution of patients in the studied groups depending on the stage of the tumor process

Stage of the tumor process	Group I		Group II		Subgroup I I a		Subgroup I I b		Whole sample	
	Abs . number b-x (%)		Abs . number b-x (%)		Abs . number b-x (%)		Abs . number b-x (%)		Abs . number b-x (%)	
I	1	**(1.43)**	0	(0.00)	0	**(0.00)**	0	(0.00)	1	0.53
THERE	3	**(4,29)**	4	(3.33)	4	**(4.35)**	0	(0.00)	7	3.68
IIB	45	**(64,29)**	59	(49,17)	57	**(61,96)**	2	(7,14)	104	54,74
IIIA	21	**(30,00)**	34	(28,33)	31	**(33,70)**	3	(10,71)	55	28,95
IIIB	0	(0,00)	17	(14,17)	0	**0**	17	60,71	17	8,95
IIIC	0	(0,00)	4	(3,33)	0	**0**	4	14,29	4	2,11
IV	0	(0,00)	1	(0,83)	0	**0**	1	3,57	1	0,53
not specified	0	(0.00)	1	(0.83)	0	**0**	1	3.57	1	0.53
Total	70	**100**	120	100	92	**100**	28	100	190	100

Analysis of cumulative survival showed (Table 2) that it was minimal in subgroup II b, maximal in group III . However, there were no significant differences between all comparison

pairs (p >0.05). Obviously, this indirectly confirms the data of other authors in favor of the fact that the treatment of lymphedema does not significantly affect the course of the oncological disease itself **[17]** .

table 2

Cumulative probability of four-year survival after surgical treatment, %			
Lifetime (years)	**The entire sample** CI95% **(N=190)**	**Group I _** CI95% **(N=120)**	**Subgroup IIa ,** CI95% **(N=92)**
1 year	98.94 (97.09÷100.00)	100 (100.00÷100.00)	100 (100.00÷100.00)
2 years	95.77 (92.9÷98.63)	94.29 (88.85÷99.72)	98.91 95.76÷100.00)
3 years	92.06 (88.22÷95.91)	91.43 (84.87÷97.99)	93.48 (88.43÷98.52)
4 years	89.42 (85.01÷93.83)	90.00 (82.97÷97.03)	89.13 (82.77÷95.49)
5 years	88.36 (83.69÷93.03)	90.00 (82.76÷97.24)	88.04 (81.38÷94.71)
Lifetime (years)	**Subgroup II b,** CI95% **(N=28)**	**Group II ,** CI95% **(N=70)**	**Significance level of group differences (p)**
1 year	92.59 (82.6÷100.00)	98.32 (95.4÷100.00)	**p>0.05**
2 years	88.89 (76.72÷100.00)	96.64 (93.41÷99.86)	**p>0.05**
3 years	88.89 (76.72÷100.00)	92.44 (87.71÷97.17)	**p>0.05**
4 years	88.89 (74.36÷100.00)	89.08 (83.42÷94.73)	**p>0.05**
5 years	85.19 (70.97÷99.40)	87.39 (81.33÷93.46)	**p>0.05**

As can be seen from Table 3, during the entire observation period, cases of VL were noted only in the control group, and more often in subgroup II a (main control) than in subgroup II b, although this difference was not statistically significant (p > 0 .05). However, when statistically comparing the zero frequency of VL in group III with its frequency in subgroup IIa , a significant difference was recorded between them (p <0.05), which we consider as evidence of the significant effectiveness of the simultaneous application of LVA during RME as a means of preventing VL in the postmastectomy period. period of the patient's life. At the same time, the activity of attendance at the control examination among patients of the compared groups did not differ statistically (p >0.05).

Table 3

Group	Number of patients	Number of cases of lymphedema , abs . (%)	Number of cases without lymphedema	Didn't show up for inspection
I	70	0 (0.00%)	59 (84.29%)	11 (15.71%)
II	120	18 (15.00%)	78 (65.00%)	24 (20.00%)
IIa	92	16 (17.39%)	56 (60.87%)	20 (21.74%)
IIb	28	2 (7.14%)	22 (78.57%)	4 (14.29%)
Total	190	18 (9.47%)	137 (72.11%)	35 (18.42%)

Table 4					
Group	Number of patients	Average terms of occurrence of hypostases (months)	Average fates of observation of patients without edema	Average periods of non-attendance for control (months)	Terms of follow-up for patients without VL and who did not appear for control and (months)
IIb	28	27.29	20.31	29.87	21.78
IIa	92	28.00	24.18	40.07	28.36
II	120	27.92	23.09	38.37	26.69
I	70	-	30.12	29.87	30.08
Total	190	27.92	26.12	35.70	28.07

According to the average time of occurrence of edema and the average time of observation of patients in whom edema was not observed, the groups did not differ statistically (Table 4). Against this background, attention is drawn to the fact that the average period of non-attendance of patients was relatively longer in subgroup IIa than in subgroup IIb and Group I. But in the aggregate, the average follow-up period for those who did not appear for the follow-up examination and patients who did not have VL (the rightmost column of Table 4) was statistically identical to that in group I. We attribute these features of the distribution of observation periods in the compared groups primarily to the fact that patients in group II b continued special treatment longer due to the greater prevalence of the process, although all of them fell under the definition of clinical group II . We also recall that we considered the observation of the patient terminated in the event of her death or departure outside the region or republic.

Table 5 Accumulation dynamics of VL cases at different five-year follow-up intervals from the moment of surgical treatment					
Annual interval number	The number of patients without signs of edema in the interval	Number of patients with signs of edema in the interval	Cumulative probability of no signs of edema in the interval, %	Shared mean error, m	Confidence limits, CI95%
Control 1 (N=92)					
1	92	**0**	100,00	1,06	95,87÷100,00
2	86	**7**	92,28	2,88	86,64÷97,92
3	73	**6**	85,38	4,13	77,28÷93,49
4	64	**2**	82,76	4,72	73,50÷92,01
5	61	**1**	81,43	4,98	71.67 ÷ 91.19
Control 2 (N=28)					
1	27	**0**	100.00	3.45	86.94 ÷ 100.00
2	27	**0**	100.00	3.45	86.94 ÷ 100.00
3	24	**2**	92.31	5.44	78.68 ÷ 100.00
4	23	**0**	92.31	5.56	78.22 ÷ 100.00
5	22	**0**	92.31	5.68	77.73 ÷ 100.00
Main group (N=70)					
1	70	0	100.00	1.39	94.63 ÷ 100.00
2	68	0	100.00	1.43	94.48 ÷ 100.00

3	64	0	100.00	1.52	94.15 ÷ 100.00
4	60	0	100.00	1.61	93.78 ÷ 100.00
5	59	0	100.00	1.64	93.68 ÷ 100.00
General control (N=120)					
1	119	**0**	100.00	0.83	96.79 ÷ 100.00
2	113	**7**	94.04	2.23	89.68 ÷ 98.41
3	97	**8**	86.98	3.42	80.28 ÷ 93.68
4	87	**2**	85.00	3.83	77.50 ÷ 92.50
5	83	**1**	83.99	4.02	76.11 ÷ 91.88
The entire sample studied (N=190)					
1	189	**0**	100.00	0.52	97,96÷100,00
2	181	**7**	96,24	1,41	93,47÷99,01
3	161	**8**	91,76	2,17	87,51÷96,01
4	147	**2**	90,52	2,42	85,78÷95,26
5	142	**1**	89,89	2,53	84,94÷94,85

We also analyzed the accumulation of VL cases in the compared groups in the post-mastectomy period (Table 5). It can be seen that the differences in this indicator between the main study group (group I) and the general control group (group II) become significant ($p < 0.05$) by the end of the third year of observation. Significant differences ($p < 0.05$) are also observed between group I and the main control (subgroup IIa) by the end of the third year of observation. During the fourth and fifth years of follow-up, these differences persist ($p < 0.05$). Thus, the preliminary results of the study allow us to draw the following conclusions.

CONCLUSION

The formed study sample statistically adequately represents the totality of patients with breast cancer for the first time identified and registered in the Samarkand region, falling under the definition of clinical group II and the clinical rationale for the use of RME. At the same time, the distributions of groups I and II by stages do not statistically differ from each other ($p>0.05$). Since the groups under study were formed in accordance with the actual practice of applying the RME in the regional branch of the RMSPTSOiR MZRUz , then this allows us to count on the fact that in the course of analyzing the results of the study, the tasks corresponding to the stated objectives of the study are completely solvable.

Carrying out RME with the imposition of LVA did not statistically affect ($p>0.05$) on the dynamics of the five-year survival of patients with breast cancer compared with the use of traditional RME. At the same time, RME with the imposition of LVA statistically significantly ($p < 0.05$) reduced the risk of developing VL in patients with breast cancer during 5 years of follow-up. The dependence of these trends on the stage of breast cancer when comparing the results in patients of group I and subgroup II b (with stages of the tumor process I - IIIA) with those of subgroup II b (in stage III b - IV) was not revealed. These data indicate the effectiveness of the application of LVA to all patients of the II clinical group, falling under the indications for the use of RME.

It seems obvious to us that the preliminary analysis confirms the high efficiency of the RME

method with simultaneous application of LVA both in terms of long-term results of treatment (by the criterion of survival probability) and maintenance of the quality of life of patients after radical treatment (in particular, by the criterion of the risk of VL).

However, the results point to the presence of untapped

It is usually tacitly assumed that the organizational reserves for maintaining the quality of life of BC patients after RME are largely associated with the development of the practice of screening and early treatment of VL in this category of patients. These reserves, obviously, can be fully realized by local health care, as long as it is provided with specialists by lymphologists . At the same time, our data indicate that this burden can be largely reduced by the use of LVA simultaneously with RME (according to Madden), which can significantly reduce the risk of VL in the post- mastectomy period.

The final conclusions on this issue can be made after a full analysis of the results of our study based on a rigorous statistical assessment of the prospects for improving the treatment of patients with breast cancer and the possibilities of screening VL in risk groups. The data obtained during this study are currently undergoing final analysis, the results of which will soon be covered in subsequent publications.

Conclusions

1. And the groups studied as part of the study of the effectiveness of the use of LVA simultaneously with the RME are formed in accordance with the actual practice of applying the RME in the regional branch of the RNPCOiR MZRUz , which will allow, in the course of analyzing the results of the study, to solve problems that correspond to the stated objectives of the study.
2. Carrying out RME with the imposition of LVA did not statistically affect ($p>0.05$) on the dynamics of the five-year survival of patients with breast cancer compared with the use of traditional RME. At the same time, RME with the imposition of LVA statistically significantly ($p < 0.05$) reduced the risk of developing VL in patients with breast cancer during 5 years of follow-up. The effectiveness of the application of LVA was shown for all patients of the II clinical group, falling under the indications for the use of RME.
3. The high efficiency of the RME method with simultaneous application of LVA was shown, which, without reducing the likelihood of survival, allows maintaining the quality of life of patients after radical treatment (according to the criterion of the risk of VL).
4. The results obtained indicate the presence of unused organizational reserves to maintain the quality of life of patients with breast cancer after RME in the framework of the development of the practice of VL screening in this category of patients.

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