WHETHER EXIST LINKS BETWEENTOXIC LIVER INJURY AND RISK OF POSTMASTECTOMIC LYMPHEDEMA IN BREAST CANCER PATIENTS?

[1]Djurayev Mirjalol Dekhanovich, [2]Uzokov Sokhib Makhsudovich, [3]Kutlumuratov Atabek Bekchanovich, [4]Esankulova Bustonoy Sobirovna

[1]DSc, professor
[2]Independent applicant
[3]DSc, professor
[4]Graduate assistant
Samarkand State Medical University, Samarkand, Uzbekistan.
Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology Tashkent, Uzbekistan.

https://doi.org/10.5281/zenodo.10063423

Abstract. *The link between risk of development at breast cancer patients (BCP) the secondary postmastectomic lymphedema (SL) on the one hand and signs which are accompanying vascular pathology (AVP), chronic gynecologic diseases (CGD) and toxic liver injury (TLI) with another hand to the moment of surgical intervention is investigated according to clinical supervision and electrocardiographic and ultrasonic researches. The link between sings of AVP and of TLI was not detected($p>0.05$). However, we observed the link between TLI and CGD($p<0.05$), but especially it was appreciable for ultrasonic signs of TLI($p<0.05$). Radical mastectomy (RME) and one-stage imposing of lymphatic-venous anastomosis effectively prevented SL during five years' of supervision, including patients with presence at them ultrasonic signs of TLI($p<0.05$). These findings are supposing prognostic value of ultrasonic investigation of patients before standard RME from the point of view of risk SL during five years' after operation.*

Keywords: *radical mastectomy, surgical, breast cancer, postmastectomic lymphedema.*

Introduction: Modern clinical medicine is characterized by a transition to the principles of multimorbid medicine [37], which is largely dictated by the increase in the second half of the last century in the proportion of chronic pathology associated with increased life expectancy [6; 15; 28]. Prevention and treatment of chronic diseases was mentioned as one of the priorities of modern medicine at the turn of the 20th-21st centuries. [22;28]. In particular, the outcome of cancer treatment is often associated with complications associated with the course of concomitant vascular pathology (CVP) [33;34]. SSP largely determines the material and labor costs of surgical treatment of cancer [31]. It should be noted that the practices of adjuvant and neoadjuvant polychemotherapy (PCT) and radiation treatment (RT) have made it possible to expand the indications for radical mastectomy (RM) to almost all stages of locally advanced breast cancer (BC) [35]. But RME itself is associated with a risk of complications,*8;9;*18]. The problem of VL is now especially significant in connection with the development of the practice of breast cancer screening, which contributes to an increase in the number of patients with indications for RME and an extension of their survival time, which accordingly brings to the fore issues of the quality of life of patients [8;9]. Strategies for early treatment and prevention of VL after RME are associated with additional burden on medical institutions and the need for constant medical

monitoring of the condition of operated patients. In this regard, we attach great importance to the surgical prevention of VL by simultaneous application of a lymphovenous anastomosis (LVA) with RME on the side of the operation. 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 the study: To evaluate the effectiveness of the RME + LVA operation on its effect on the risk of developing VL after RME in patients with breast cancer, their five-year survival and the relationship of this risk with the signs of SSP and gynecological pathology and the condition of the liver (according to its sonographic examination), identified before the operation.

Materials and methods. Main andThe study sample was formed from a population of patients with stage II breast cancer. groups, first identified in the Samarkand region in 2017-2020, the treatment of which included RME for various clinical indications -in accordance with the currently accepted ideas about primary operable (locally advanced) and primary inoperable cancer. HThe population of this population amounted to 1078 cases of breast cancer. The main sample included the following groups of patients: group I was formed prospectively – 70 patients with stage I-IIIA breast cancer, operated on according to the “RM+LVA” scheme; II – control group of 120 patients, compiled retrospectively by random selection from a total of 1078 patients treated according to the “RME without LVA” regimen. Group II consisted of 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 and secondary, metachronous breast cancer (23.33%group II).

In addition, during the main study, an additional group (AG) was retrospectively composed of 44 patients with breast cancer in whom signs of VL were detected during the control period (CP - from 01/01/2017 to 07/01/2022). The DG included 18 patients from group II and 26 from an additional sample (180 patients with breast cancer), obtained by the same random selection from the remaining 888 patients of the total population of patients with class II breast cancer. gr. (1078-(120-70)=888). The total number of cases of VL among 300 patients with breast cancer in a retrospective sample (120+180=300) was 44 (44*100%/300=14.7%). Thus, the total volume of the studied sample was 216 patients with breast cancer (190+26=216), whose complex or combined treatment scheme included the operations “RME without LVA” or “RME + LVA”.

LVA application methoddescribed by us previously [38]. Current clinical standards were used [Collection of standards and..., 2017]. 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 (on SIMVIEW NT installations from the German company Siemens and THERATRON - 780E from the Canadian company MDS - nordion). Topometric maps were calculated based on data from X-ray simulation, P-X-ray, computed tomography (CT, MRI), endoscopic and sonographic (ultrasound) studies.

At the end of special treatment, patients were given standard recommendations for appearing for control. Their timely attendance at the follow-up examination was recorded. In case of failure to appear, the facts and reasons for their seeking medical help were identified remotely, through the clinic at the place of residence. Observation was considered completely terminated in

the event of the death of the patient or her complete withdrawal from direct observation (due to travel outside the region or republic). Facts 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 [16; 20; 23; thirty; 32; 36].

Research results and discussion:

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

Table 1

Proportional average cases of VL and failure of patients to appear for control during the CP (% 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%)

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 CP 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, There was no remote data, at their place of residence, about the occurrence of signs of VL 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).

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	without overhead line	those who did not show up for control	no data on VL + 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	without overhead line	those who did not show up for control	no data on VL+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 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 5-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 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 - per the moment of their last appearance for the control examination.
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, group I and subgroup IIa had similar indicators - 10.0% and 9.8%.

There were no statistically significant differences between the groups in the proportion of patients who did not show signs of complications when appearing for a follow-up examination (p>0.05) during the CP, 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 CP: in patients of group I, where no cases of VL were detected during CP: 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 5a givesdistribution of patients according to the characteristics of seven nosological units of the SSP at their last appearance during the CP. In Table 5b, the same data are presented with recalculation for the distribution of ERP signs in group II, accepted as the “standard” against which intergroup comparisons were made.

If you do not pay attention to the rightmost column of the table (with data for DG), then there are no statistically significant differences between groups I, II, IIa and IIb (p>0.05), in including according to the data of recalculation to the “standard”. Without taking into account the data on DG, the results of such a comparison do not allow us to state that the risk of VL after RME is directly linked to SSP in patients with breast cancer, as a number of authors believe [3; eleven; 13; 17; 21; 24; 26; 27]; It also cannot be said that the risk of VL is not associated with SSP. Without taking into account the distribution of SSP signs in the DH, the assumption arises that, at least in part, the relationship between SSP and the risk of VL that develops after RME is determined by the degree of involvement of the SSP and lymphatic systems in the compensatory reactions of the body after RME, and directly the risk of VL not associated with SSP. Obviously, further research is needed to clarify the issue of the relationship between SSP and the risk of VL after irradiation.

In particular, some light on the question of the connection between the risk of VL and SP is shed by parallel data on the distribution of SSP in the DH.

The DG was composed of patients in whom signs of VL were detected during the CP. Comparingfractional average distributions of patients with DH according to the signs of seven nosological units of SP in the main studied groups, it can be noted that there are statistically significant differences between the main study groups (I, II, IIa and IIb) on the one hand and DH on the other only in relation to the frequency of signs of stage IIb HD ($p<0.05$). It seems that the risk of the appearance of signs of VL after RME in patients with breast cancer is associated with their low grade IIb hypertension, while this risk is not reliably associated with the signs of the other six SSP. But when recalculating the specific weights of the characteristics of each ERP to their "standard" structure (Table 5b), the statistical significance of intergroup differences is completely leveled out ($p>0.1$). Differences between the fractional average GB IIb st. in the DH and that in the other groups is statistically insignificant ($p>0.05$). Apparently, the relationship between the signs of ERP, identified before RME, and VL developing after RME are determined by the degree of involvement of the cardiovascular and lymphatic systems in the body's compensatory reactions to RME. Apparently, the persistence of hypertension is somehow related to the persistence of edema, possibly through a failure of the compensatory abilities of the lymphatic vasculature on the side of surgery in patients with breast cancer. From tables 6a,b,c it is clear that the fractional averages of the number of cases with the presence of signs of SSP (at least one of the nosologiesIBS, AS, KKS, SK, ASGM, GBIIabst. and NDC) among patients with DH on the one hand and lobar averages in groups I and II without the development of VL during the CP on the other (70 patients in I and 102 patients in II, of which 76 in IIa and 26 in IIb) did not differ statistically significantly between them ($p>0.05$). Obviously, in order to understand the significance of SSP in the genesis of VL after RME, careful further studies are needed.

Table 6a

The total proportion of patients with a sign of SSP (at least one of the diagnoses of IHD, KS, CS, AS or AGM) depending on the development or absence of signs of VL after surgery

Group	Number of b-x in the group	Number of b-x with SSP	M+m,%	CI95%
Group 1 (RME+LVA, with without VL)	70	36	51.43+5.97	39.72÷63.14
Group 2 (breast cancer, with VL)	44	21	47.73+7.53	32.97÷62.49
Group 3 (BC, without VL)	102	65	63.73+4.76	54.39÷73.06
Group 3a (breast cancer, without VL)	76	48	63.16+5.53	52.31÷74.00
Group 3b (breast cancer, without VL)	26	17	65.38+9.33	47.10÷83.67

Table 6b

Proportion of patients with signs of stage IIab hypertension. depending on the development of VL after RME

Group 1 (RME+LVA, with without VL)	70	24	34.29+5.67	23.17÷45.41
Group 2 (breast cancer, with VL)	44	16	36.36+7.25	22.15÷50.58
Group 3 (BC, without VL)	102	26	25.49+4.32	17.03÷33.95
Group 3a (breast cancer, without VL)	76	14	18.42+4.45	9.71÷27.14

Group 3b (breast cancer, without VL)	26	12	46.15+9.78	26.99÷65.32

Table 6c

Proportion of patients with signs of NCD depending on the development of VL after RME				
Group 1 (RME+LVA, with without VL)	70	32	45.71+5.95	34.04÷57.38
Group 2 (breast cancer, with VL)	44	18	40.91+7.41	26.38÷55.44
Group 3 (BC, without VL)	102	44	43.14+4.90	33.53÷52.75
Group 3a (breast cancer, without VL)	76	36	47.37+5.73	36.14÷58.59
Group 3b (breast cancer, without VL)	26	8	30.77+9.05	13.03÷48.51

We also drew attention to the availability of medical reports on the condition of the internal organs, taking into account instrumental data, in particular, data from an ultrasound examination conducted in accordance with the standards used by the surgical department of the regional branch of the RSMNPCIOiR of the Ministry of Health of the Republic of Uzbekistan. We assume that they may shed additional light on understanding the nature of the risk of VL after RME. Here we are talking about the presence of signs of chronic pathology of the organs of the reproductive system (gynecological diagnoses - chronic diseases of the body and cervix and ovaries) and liver ("fatty degeneration" or "diffuse changes in the liver parenchyma", considered a consequence of the toxic effect on it), observed in CP flow. From among the 216 patients in the general sample, we formed a special sample of patients whose abdominal organs were examined by ultrasound. It included the following three additional groups of patients (examined by ultrasound): DG I - 36 patients with signs of VL that developed during the CP, treated surgically according to the "RME without LVA" scheme; DG II - 79 patients (all without signs of VL) from control group II, treated according to the "RME without LVA" regimen; DG III - 65 patients from group I, treated according to the "RME + LVA" scheme.

The results are shown in Table 7.

Table 7

Distribution of breast cancer patients according to signs of gynecological diseases and degenerative changes in the liver during ultrasound studies in additional groups before surgical treatment

Group	Number of patients	M+m%	CI95%
DG I(patients with VL after RME without LVA) (N=36)			
Gynecological diseases	19	52.8+1.2	50.36÷55.20
Ultrasound - Dystrophic changes in the liver	10	27.8+1.2	25.38÷30.17
DG II(patients without VL after RME without LVA) (N=79)			
Gynecological diseases	39	49.4+1.2	47.04÷51.70
Ultrasound - Dystrophic changes in the liver	26	32.9+1.2	30.60÷35.23
DG III(patients without VL with RME+LVA) (N=65)			
Gynecological diseases	15	23.1+1.2	20.76÷25.39
Ultrasound - Dystrophic changes in the liver	26	40.0+1.2	37.65÷42.35

Dystrophic phenomena in the liver parenchyma were statistically significantly more often detected using ultrasound among patients in the DG-III group than in DG-I ($p<0.05$) and DG-II ($p<0.05$). At the same time, in patients with DG-I, degenerative phenomena in the liver were observed significantly less often than in patients with DG-II ($p<0.05$), although this difference is almost on the verge of significance ($p<0.05$). It is curious that in patients with DG-I, signs of gynecological pathology were detected significantly more often ($p<0.05$) than in the DG-III group. It is still difficult to give an unambiguous explanation for these facts. But we admit that they may be relevant to predicting the risk of VL after surgical treatment of breast cancer. But we consider these facts worthy of careful research in the future, first of all - their stable reproducibility and their causal explanation.

In general, the results obtained are consistent with the idea of using RME+LVA surgery to prevent VL and preserve the quality of life of patients with breast cancer. This seems very important, in particular from the point of view of coordinating the activities of oncology and lymphology servicesin the region. In any case, the nature of the study and its results allow us to count on a good effect on a population scale from the widespread use of the RME + LVA operation.The freed up medical time and funds can be used to further improve the oncological and mammological services in the region.

Conclusions:

1. The data obtained on the effectiveness of RME+LVA surgery as a means of preventing VL, which does not statistically significantly affect the probability of five-year survival, the course of the main process and concomitant vascular pathology, allows us to count on a positive effect on a population scale from the widespread use of its use. This would make it possible to use the freed-up medical time and funds for further improvement of oncological and mammological services in the region and their coordinated functioning.

2. Dystrophic phenomena in the liver were observed significantly more often in patients after RME+LVA than in patients with RME without VL, and even more often than in patients with RME without LVA with the development of signs of VL. In patients with VL treated with “RME without LVA,” degenerative phenomena in the liver were observed significantly less frequently than in patients without signs of VL treated with the same method. In patients with VL after “RME without LVA”, signs of gynecological pathology were significantly more often detected than in patients without VL after the same treatment, and then in patients after “RME + LVA”. It is assumed that both groups of facts may be associated with the reasons for the development of VL after surgical treatment of breast cancer, which remains to be clarified in the future.

REFERENCES

1. Allegra C. Morphological and functional changes of the microlymphatic network in patients with advancing stages of primary lymphedema / C. Allegra, R. Sarcinella, MJ Bartolo // Lymphology. - 2002. - Vol. 35. No. 3.- P. 114-120.
2. Asdourian MS, Skolny MN, Brunelle C. ea Precautions for breast cancer-related lymphoedema: Risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. Lancet Oncol 2016; 17:e392-405.
3. Aspelund A., Robciuc MR, Karaman S. ea Lymphatic System in Cardiovascular Medicine. Circ. Res. 2016, 118, 515–530.

4. Cormier JN, Askew RL, Mungovan KS ea Lymphedema beyond breast cancer: A systematic review and meta-analysis of cancer-related secondary lymphedema. Cancer 2010, 116, 5138–5149.
5. DiSipio T., Rye S., Newman B. ea Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. Lancet Oncol 2013;14:500-15.
6. Fabbri E., Zoli M., GonzalezFreire M.ea Aging and Multimorbidity: New Tasks, Priorities, and Front Tiers for Integrated Gerontological and Clinical Research. Journal of the American Medical Directors Association. 2015;16(8):640–7. DOI:10.1016/j.jamda.2015.03.013.
7. Ferguson CM, Swaroop MN, Horick N.eaImpact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. J Clin Oncol 2016;34:691-8.
8. Gillespie TC, Sayegh HE, Brunelle CL ea Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. Gland Surg 2018;7(4):379-403.
9. *Grada AA, Phillips TJ (December 2017). "Lymphedema: Diagnostic workup and management".Journal of the American Academy of Dermatology. 77(6):995-1006.*
10. Kim M., Kim SW, Lee SU ea A model to estimate the risk of breast cancer-related lymphedema: Combinations of treatment-related factors of the number of dissected axillary nodes, adjuvant chemotherapy, and radiation therapy // Int. J. Radiat. Oncol. Biol. Phys., 2013;86:498-503.
11. Lim HY, Thiam CH, Yeo KP ea Lymphatic vessels are essential for the removal of cholesterol from peripheral tissues by SR-BI-mediated transport of HDL. // Cell Metab., 2013, 17, 671–684.
12. Lymfo-Veneuse Anastomosen Ter Preventie Van Lymphoedem. University Hospital, Ghent.: https://ichgcp.net/ru/clinical-trials-registry/NCT05601037
13. Martel C., Li W., Fulp B. ea Lymphatic vasculature mediates macrophage reverse cholesterol transport in mice. J. Clin. Investing. 2013, 123, 1571–1579.
14. Mortimer PS, Rockson SG New developments in clinical aspects of lymphatic disease. J. Clin. Investig. 2014, 124, 915–921.
15. Omran AR The epidemiologic transition: a theory of the epidemiology of population change. Milbank Memorial Fund Quarterly, 1971, 29: 509–538.
16. Parkin D., Hakulinen T. Analysis of survival. In: Jensen OM, Parkin DM, MacLennan R, Muir CS and Skeet RG (eds) Cancer Registration, Principles and Methods. IARC Sci. Publ. No. 95. IARC Press, Lyon, 1991; pp. 159–176.
17. Randolph GJ; Miller NE Lymphatic transport of high-density lipoproteins and chylomicrons. J. Clin. Investig. 2014, 124, 929–935.
18. Sayegh HE, Asdourian MS, Swaroop MNeaDiagnostic methods, risk factors, prevention, and management of breast cancer-related lymphedema: Past, present, and future directions. Curr Breast Cancer Rep 2017;9:111-21.
19. Shah C., Vicini FA Breast cancer-related arm lymphedema: Incidence rates, diagnostic techniques, optimal management and risk reduction strategies. Int J Radiat Oncol Biol Phys 2011; 81:907-14.
20. Siegel R., Naishadham D., Jemal A. Cancer Statistics, 2013 // CA Cancer J. Clin. - 2013; 63:11-30.

21. Small DM, Bond MG, Waugh D. ea Physicochemical and histological changes in the arterial wall of nonhuman primates during progression and regression of atherosclerosis. J. Clin. Investig. 1984, 73, 1590–1605.
22. Starfield B., Lemke KW, Bernhardt T. Comorbidity: Implications for the Importance of Primary Care in Case Management // Ann Fam Med, 2003; 1(1):8-14.
23. Swaminathan R., Brenner H. Statistical methods for cancer survival analysis // IARC Scientific Publications volume 162, ISBN 978-92-832-2162-3, Lyon, International Agency for Research on Cancer, 2011.
24. Telinius N., Hjortdal V.E. Role of the lymphatic vasculature in cardiovascular medicine. Heart 2019, 105, 1777–1784.
25. Tsai RJ, Dennis LK, Lynch CF ea The risk of developing arm lymphedema among breast cancer survivors: A meta-analysis of treatment factors. Ann Surg Oncol 2009;16:1959-72.
26. Vuorio T., Nurmi H., Moulton K. ea Lymphatic vessel insufficiency in hypercholesterolemic mice alters lipoprotein levels and promotes atherogenesis. Arter. Thromb. Vasc. Biol. 2014, 34, 1162–1170.
27. Wang X., Rader DJ Molecular regulation of macrophage reverse cholesterol transport. Curr. Opin. Cardiol. 2007, 22, 368–372.
28. Dilman V.M. Four models of medicine. / L.: Medicine. – 1987.
29. Zalutsky I.V., Antonenkova N.N., Zhukovets A.G. Complex treatment of patients with postmastectomy lymphedema of the extremities using lymphatic drainage operations / I.V. // Annals of plastic, reconstructive and aesthetic surgery. - 2002. - No. 4. - P. 50-51.
30. Ivanov O.A. Method for processing a database of cancer patients (survival): Method. Recommendations. – M. – 1997. – p.97.
31. Kolomiets E. A., Kurmukov I. A., Sandomirskaya A. P., Kashiya Sh. R. Comorbidity in oncology: results of preoperative examination of patients in a specialized oncology clinic / Abstracts of the XXI Russian Oncology Congress. // Malignant tumors. – 2017, V.7, No. 3, 1s. – P.171-172. http://www.malignanttumours.org.
32. Lakin G.F. Biometrics. – M.: Higher. school. – 1990. – 352 p.
33. Magomedov O.M., Magomedova P.O., Magomedov G.M. Cardivascular complications in the treatment of breast cancer // Russian Journal of Cardiology 2010. - No. 1 (81). -– pp. 73-76.
34. Mamedov M.N., Badeinikova K.K., Karimov A.K. Targets for the prevention of comorbidity of cardiovascular diseases and cancer // Russian Journal of Cardiology 2022;27(11): 5235. P.115-120; doi:10.15829/1560-4071-2022-5235;https://russjcardiol.elpub.ru.
35. Collection of standards and clinical protocols for the diagnosis and treatment of malignant cancer / Team of compilers, ed. prof., doctor of medical sciences M.N. Tillyashaikhova. - Tashkent. - 2017. – 254 p.
36. Strelkov R.B. Statistical tables for express calculations of the standard error and confidence limits at zero or one hundred percent value of experimental and clinical data indicators / MZSSSR, AMNSSSR, Scientific Research Institute of Med. Radiol. - Obninsk, 1982. – 45 p.
37. Tarlovskaya E.I. Comorbidity and multimorbidity are a modern interpretation and pressing challenges facing the therapeutic community. // Cardiology. 2018; 58(S9): 29–38.

38. Uzakov S.M., Juraev M.D., Karimova M.N. Modern ideas about post-matectomy lymphedema, methods of its treatment and prevention (literature review) // Journal of Biomedicine and Practice - No. 1 (2022) – P. 179-188. DOIhttp://dx.doi.org/10.26739/2181-9300-2022-1.