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SPHINGOSINE-1-PHOSPHATE AS A NEW DIAGNOSTIC, PROGNOSTIC BIOMARKER FOR PROSTATE CANCER AND EFFECTIVENESS OF INTENSITY-MODULATED RADIATION THERAPY

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Sphingosine-1-phosphate have long been implicated in different biological processes including cell migration, proliferation, and cell death. Our hypothesis is based on the possible role of sphingosine-1-phosphate as a biomarker of poor prognosis in prostate cancer and effectiveness of intensity-modulated radiation therapy. The Tomo System there were treated 41 patients with locally advanced cancer prostate. To determine free sphingosine, we used a method based on the extraction of sphingoid bases with diethyl ether, in our modification. The levels of normal tissue sphingosine-1-phosphate are significantly higher as compared with prostate cancer. There is a significant correlation between plasma prostate-specific antigen and tumor tissue sphingosine-1-phosphate in prostate cancer. Sphingosine-1-phosphate is synthesized in the tumor tissue of prostate cancer 2-fold less than in the surrounding tumor tissue. After radiation therapy, its level in the prostate tumor increases 3-fold, and in the tissue surrounding the tumor 1.5-fold, which indicates the development of the radiation-induced bystander effect. Our data provide the first evidence that tumor tissue sphingosine-1-phosphate is a significant prognostic marker for prostate cancer mortality.

Key words: sphingosine-1-phosphate, prostate cancer, radiation therapy.

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СФІНГОЗИН-1-ФОСФАТ ЯК НОВИЙ ДІАГНОСТИЧНИЙ, ПРОГНОСТИЧНИЙ БІОМАРКЕР РАКУ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ ТА ЕФЕКТИВНОСТІ ІНТЕНСИВНО-МОДУЛЬОВАНОЇ РАДІОТЕРАПІЇ

Сфінгозин-1-фосфат бере участь у різних біологічних процесах, включаючи міграцію клітин, проліферацію та загибель клітин. Наша гіпотеза заснована на можливій ролі сфінгозин-1-фосфату як біомаркера несприятливого прогнозу при раку передміхурової залози та ефективності променевої терапії з модульованою інтенсивністю. За системою Томо System пролікований 41 хворий на місцево поширений рак передміхурової залози. Для визначення вільного сфінгозину використовували метод, заснований на екстракції сфінгоїдних основ діетиловим ефіром, нашої модифікації. Встановлено, що рівні сфінгозин-1-фосфату в нормальних тканинах значно вищі порівняно з раком передміхурової залози. Існує значна кореляція між простато-специфічним антигеном плазми та сфінгозин-1-фосфатом пухлинної тканини при раку передміхурової залози. Сфінгозин-1-фосфат синтезується в пухлинній тканині раку передміхурової залози в 2 рази менше, ніж у навколишній пухлинній тканині. Після променевої терапії його рівень у пухлини передміхурової залози збільшується в 3 рази, а в навколишній пухлину тканини в 1,5 раза, що свідчить про розвиток радіаційно-індукованого ефекту свідка. Наші дані є першим свідченням того, що сфінгозин-1-фосфат пухлинної тканини є значним прогностичним маркером смертності від раку передміхурової залози.

Ключові слова: сфінгозин-1-фосфат, рак передміхурової залози, променева терапія.

The study is a fragment of the research projects "Development and implementation of innovative technologies for the diagnosis of oncogynecological and oncourological diseases based on liquid biopsy data of extracellular DNA and stem cells", state registration No. 0123U101248 and "Biomarker diagnostics of oncourological diseases", state registration No. 0118U001025.

Sphingolipids, such as ceramide, ceramide 1-phosphate (C1P), glucosylceramide, sphingosine, and sphingosine-1-phosphate (S1P), have long been implicated in different biological processes including cell migration, proliferation, and cell death [6, 7, 14]. S1P is a lysophospholipid mediator found in the blood which has been shown to participate in a wide range of biological responses, including stimulation of cell proliferation, inhibition of apoptosis and regulation of cell shapes and motility. Biological activities of S1P are mediated through the S1P receptors, a family of G protein-coupled cell surface receptors [15]. Studies over the years have highlighted the significance of sphingolipids in human diseases including but not limited to lysosomal storage diseases, autoimmune diseases, cardiovascular diseases, infectious diseases, inflammation, COVID-19 and cancer [7, 14]. The dysregulation of sphingolipid metabolism in various human cancer types suggests that bioactive sphingolipids are vital for tumor growth and survival [7].

Prostate cancer (PCa) is the third most common cancer worldwide, and the second most common cancer among men [12, 13]. Escape of prostate cancer (PCa) cells from ionizing radiation–induced (IR-induced) killing leads to disease progression and cancer relapse. The influence of sphingolipids, such as ceramide and its metabolite sphingosine 1-phosphate, on signal transduction pathways under cell stress is important to survival adaptation responses [3].

Over the past decade, with the advent of advanced CT-based treatment, planning intensity modulated radiotherapy has gained ascendency over other radiation approaches for primary prostate cancer treatment [3, 4, 8]. For patients who have not undergone prostatectomy, radiation therapy involves a treatment course of greater than 70 Gy usually administered in daily fractions of 1.8 to 2 Gy over a 7- to 9-week period. Therefore, for purposes of better control of such patients, the molecular mechanisms underlying PCa cell radioresistance and methods to interdict such resistance must be understood in order to maximize the curative potential of radiation therapy [3].

Our hypothesis is based on the possible role of sphingosine-1-phosphate as a biomarker of poor prognosis in prostate cancer and effectiveness of intensity-modulated radiation therapy.

The purpose of the study was to investigate the association between tissues sphingosine-1-phosphate and overall survival in patients with prostate cancer.

Materials and methods. The studies were carried out on the basis of city and regional hospitals of the Luhansk region and Ukrainian Center of Tomotherapy, Kropyvtskyy between 2015 to 2021. In accordance with the provisions of the Declaration of Helsinki by the World Medical Association of the last revision and informed consent for the use of biological material was obtained in all patients prior to inclusion in the study. Research permission was obtained from the Bioethics Committee of the Lugansk State Medical University (Rubizhne, Ukraine, number 25/2015).

The patients' epidemiological data, laboratory examination, complications, clinical outcomes, and treatment plan were extracted from medical records.

Of total, only those patients with prostate-specific antigen (PSA) levels between 0.66–92 ng/mL, a Gleason score between 5–10, and a clinical stage defined as T3a, or T3b were considered, yielding 98 subjects. We retrospectively reviewed the clinical data of 98 high-risk prostate cancer patients who underwent radiotherapy. Biochemical recurrence of disease was defined in accordance with the Phoenix criteria (PSA ≥ PSA nadir +2 ng/ml) [2, 4].

A prerequisite for summing up the image-guided radiotherapy technology (IGRT) intensity-modulated radiation therapy (IMRT) is the IGRT technique (radiation therapy under image guidance). These conditions are met by the Tomotherapy System (Tomo HD), presented in Ukrainian Center of Tomotherapy, Kropyvtskyy.

The material for the study was cancerous tissue (n=21), peri-tumor normal prostate tissue (n=21) of patients without prostate radiation therapy after prostatectomy. As well as adenocarcinoma tissue (n=21) and tissue surrounding the tumor (n=21) after tomoradiotherapy. Cancerous tissue, peri-tumor normal prostate tissue and normal prostate tissue distant from the cancer were collected from surgical specimens immediately after operation, excised and frozen in liquid nitrogen. Tumor and adjacent normal tissues were collected in microcentrifuge tubes and flash-frozen in liquid nitrogen immediately after surgical resection. Approximately 50 mg of tissue was homogenized in a cold sucrose isolation medium (0.25M sucrose, 1mM EDTA, pH=7). The levels of S1P were determined exactly as previously described [1, 9]. Total protein was quantitated using Bradford's reagent (Bio-Rad Laboratories, Hercules, CA).

Data Processing. Statistical and graphical analyses were done using STATISTICA 7.0 (StatSoft Inc. USA, version 7.0) and and MedCalc Version 20.218 64 bit (MedCalc Software, Ostend, Belgium). Parametric data were summarized as mean (standard error) (Mean±SEM). Kolmogorov–Smirnov test was applied to examine the normality of data distribution. To examine group-wise differences, unpaired Student's t-test was used. Nonparametric results are expressed as median (Me) and interquartile range (IQR). The difference between study groups was tested by a nonparametric Mann–Whitney U test was used. Receiver operating characteristics (ROC) curve analysis was performed to estimate optimal cut-off values, maximizing sensitivity and specificity according to the Youden index. Survival analysis was performed using the Kaplan–Meier method; univariate and multivariate analyses were undertaken using log rank test and Cox's regression model, respectively. A *p*-value below 0.05 was considered statistically significant. The Cox proportional hazards regression model was used to assess the effect of serum PSA and Sphingosine-1-phosphate levels on clinical outcomes in survival analysis.

Results of the study and their discussion. A total of 42 PCa patients were included in the study. The median age was 69.5 (IQR: 65–76) years. Circulating levels of serum PSA and sphingosine-1-phosphate of PCa-tumor tissue before and after Tomotherapy were measured in samples of PCa patients or control patients with no history of cancer (*n*=20), and correlated with the clinical stage and grade (Table 1).

Levels of S1P were significantly higher (2-3-fold higher) in peri-tumor normal tissue than in PCa-tumor tissue before Tomotherapy (56.18±1.83 nmol per mg protein *vs* 19.71±1.63 nmol per mg protein, $p<0.000001$) and after Tomotherapy (67.42±2.06 nmol per mg protein *vs* 48.57±1.74 nmol per mg protein, $p<0.000001$). Serum PSA decreased in patients with prostate cancer 1 month after Tomotherapy by 9-fold (2.97 ng/ml IQR 2.0 – 4.42 *vs* 18.48 ng/ml IQR 12.68 – 40.0, $p<0.000001$).

Table 1

Levels of serum PSA and Sphingosine-1-phosphate in prostate cancer patients who underwent radiotherapy

Clinical groups	Serum PSA, ng/ml			Sphingosine-1-phosphate, nmol/mg of protein tissues
	Median	Q_{25}	Q_{75}	Mean±SEM
healthy donors (control group) (n=20)	0.9	0.32	1.18	
patients with PCa (n=21)	18.48	12.68	40.0	
Kruskal-Wallis test	$p^1 < 0.000001$			
Mann-Whitney U Test	$p^1 < 0.000001$			
patients with PCa after Tomotherapy (n=21)	2.97	2.0	4.42	
Kruskal-Wallis test	$p^1 = 0.02496$ $p^2 = 0.000299$			
Mann-Whitney U Test	$p^1 < 0.000001$ $p^2 < 0.000001$			
PCa-tumor tissue (n=21)				19.71±1.63
PCa-peri-tumor normal tissue (n=21)				56.18±1.83
				$p^3 < 0.000001$
PCa-tumor tissue after Tomotherapy (n=21)				48.57±1.74
				$p^3 < 0,000001$ $p^4 = 0.004484$
PCa-peri-tumor normal tissue after Tomotherapy (n=21)				67.42±2.06
				$p^3 < 0.000001$ $p^4 = 0.000208$

Notes: PSA – Intergroup by the Mann–Whitney U test. p^1 – significant differences between control group and test groups. ^{2} – significant differences between patients with PCa and patients with PCa after Tomotherapy. SP1 data are means ± SEM for Gaussian variables. Intergroup by the T-test Students. p^3 – significant differences of SP1 between tumor tissue and test groups. p^4 – significant differences of SP1 between peri-tumor normal tissue and test groups.

The Spearman non-parametric correlation was used to investigate the correlation between plasma level PSA in patients PCa and sphingosine-1-phosphate of PCa-tumor tissue before and after Tomotherapy. The correlation coefficients between plasma level PSA and S1P of PCa-tumor tissue showed astrong and negative correlation (p =0.0001, *r* =-0.737). In addition, the correlation coefficient between plasma level PSA after Tomotherapy and S1P of PCa-tumor tissue has a moderate and negative correlation (p =0.001, *r* =-0.674). The S1P of PCa-tumor tissue coefficient had a moderate and negative correlation (p =0.007, *r* =-0.587) with S1P-PCa-peritumor normal tissue. The correlation of S1P-PCa-peritumor normal tissue and S1P-PCa-tumor tissue after Tomotherapy were not significant (p =0.048, *r* =-0.448).

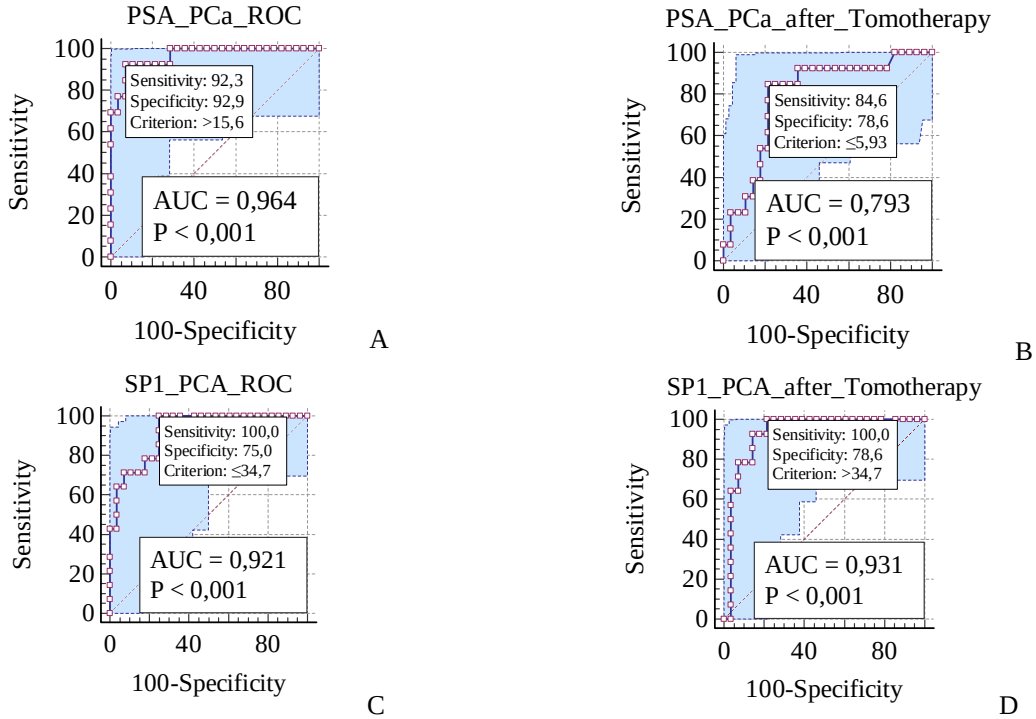

Fig. 1. ROC analysis: receiver operating characteristic (ROC) curves for PSA and Sphingosine-1-phosphate measured in a) PSA-patients with PCa; b) PSA-patients with PCa after Tomotherapy; c) S1P-patients with PCa; d) S1P-patients with PCa after Tomotherapy.

Note: Here and in the following figures: p<0.001 – calculated by univariate logistic regression analysis.

Patient age was not correlated with PSA (p =0.498, *r* =0.16), PSA after Tomotherapy (p =0.422, *r* =-0.19), S1P of PCa-tumor tissue (p =-0.3, *r* =0.196), S1P of PCa-tumor tissue after Tomotherapy (p =0.147, *r* =0.54).

ROC-analysis was used to evaluate the diagnostic performance of serum PSA profile in the differentiation between control group (healthy donors) and patients with PCa befor and after Tomotherapy (Fig.1, Table 2).

Table 2

The sensitivities, specificities and the cut-off value of PSA and Sphingosine-1-phosphate levels in patients with PCa

Groups		cut-off value	Area, AUC	Sensi-tivity	95% CI	Speci-ficity	95% CI	p-value
Serum PSA. ng/ml	patients with PCa	>15.6	0.964	92.31	64.0–99.8	92.86	76.5–99.1	<0.0001
	patients with PCa after Tomothe-rapy	≤5.93	0.793	84.62	54.6–98.1	78.57	59.0–91.7	<0.0001
Sphingosine-1-phosphate, nmol/mg of protein tissues	PCa-tumor tissue	≤34.7	0.921	100.0	76.8–100.0	75.0	55.1–89.3	<0.0001
	PCa-tumor tissue after Tomothe-rapy	>34.7	0.931	100.0	76.8 –100.0	78.57	59.0–91.7	<0.0001

With respect to survival, the optimal cut-off values identified by ROC analysis were as follows: PSA of patients with PCa, 15.6 ng/ml; PSA of patients with PCa after Tomotherapy, 5.93 ng/ml; S1P PCa-tumor tissue, 34.7 nmol/mg of protein tissues; S1P PCa-tumor tissue after Tomotherapy, 34.7 nmol/mg of protein tissues. The values of area under the curve (AUC) were 0.964 (0.854 to 0.998) for PSA of patients with PCa; 0.793 (54.6 to 98.1) for PSA of patients with PCa after Tomotherapy; 0.921 (76,8 to 100,0) for sphingosine-1-phosphate of PCa-tumor tissue; 0.931 (76,8 to 100,0) for sphingosine-1-phosphate of PCa-tumor tissue after Tomotherapy. The median follow-up was 45.0 months (95 % CI range=20.04 to 60.0 months). Five-year overall survival was 68.29 % (Fig.2).

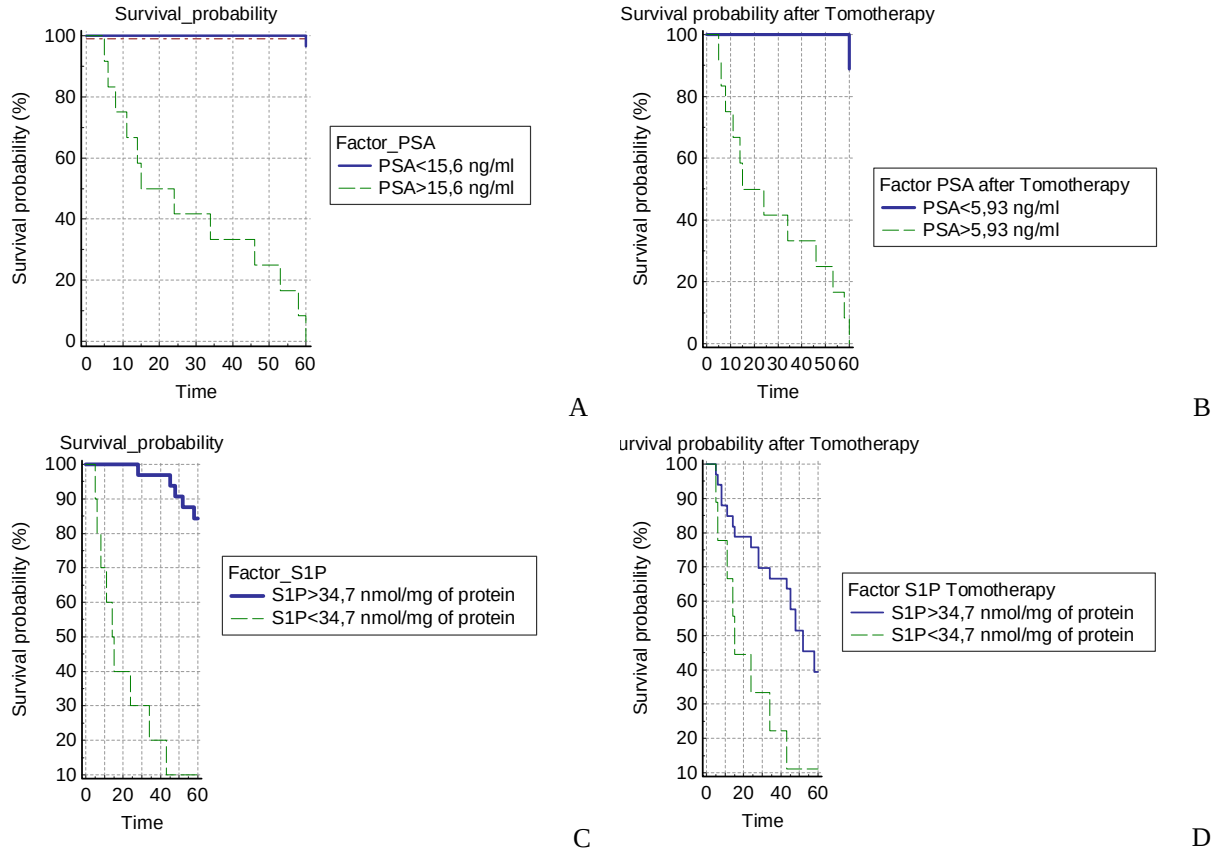

Fig. 2. Kaplan–Meier survival curves of PCa patients with different cut-off values of the of indexes investigated: a) PSA-patients with PCa; b) PSA-patients with PCa after Tomotherapy; c) S1P-patients with PCa; d) S1P-patients with PCa after Tomotherapy. p value by Long-rank test.

The Kaplan–Meier survival curves, after classifying the patients on the basis of Youden cut-offs obtained by ROC curves, showed significant lower survival with higher values of PSA of patients with PCa (HR = 348.05; 95 % CI 76.9 to 1575.1, p = 0.0001), PSA of patients with PCa after Tomotherapy (HR

= 16.7; 95 % CI 7.03 to 39.57, p < 0.0001), S1P PCa-tumor tissue (HR = 16.7; 95 % CI 7.03 to 39.57, p < 0.0001), S1P of PCa-tumor tissue after Tomotherapy (HR = 4,62; 95 % CI 1,46 to 14,58, p < 0.0091).

Next, we performed a Cox proportional hazards regression analysis of predictors of progression to PSA levels. On univariate analyses, PSA before Tomotherapy ≥15.6 ng/mL (p=0.0001) and PSA nadir after Tomotherapy ≤5.93 ng/mL (p=0.0001) were significantly associated with an increased risk of poor prognosis of overall survival.

These data were also confirmed in a multivariate analysis. Estimates of the HR adjusted for pre-Tomotherapy PSA (<15.6 ng/ml versus >15.6 ng/ml) also confirmed these results (HR 101.9 [95 % CI 12.37 – 839.47], p<0.0001). On multivariate analyses, PSA after Tomotherapy ≤5.93 ng/mL was a significant prognosticator (HR 8.89 [95 % CI 2.24–35.27], p= 0.0029).

We show that the levels of normal tissue S1P are significantly higher as compared with PCa. Furthermore, there is a significant correlation between plasma PSA and tumor tissue S1P in PCa. Finally, our data provide the first evidence that tumor tissue S1P is a significant prognostic marker for PCa mortality. We have identified prostate tissue as the major source of S1P in our patients and shown a highly significant downregulation of circulating PSA in PCa patients compared with control counterparts. The authors Nunes J, et al. have previously shown that, the potential of S1P to have a role as a plasma marker of human disease has been recently demonstrated by a study, which showed that plasma S1P was elevated in patients with prostate cancer [11]. The fact that circulating S1P levels were lower in advanced PCa patients led the researchers to conclude that this ruled out the possibility of S1P originating from cancer cells. However, our study showed that S1P is synthesized both in the tumor tissue of adenocarcinoma of the prostate and in the tissues surrounding the tumor. Moreover, S1P is synthesized in the tumor tissue 2-fold less than in the surrounding tissue. And after radiation therapy, its level in the tumor increases 3-fold, and in the surrounding prostate tissue too.

Overall, in this study we provide the first evidence that both plasma PSA and prostate tumor tissue S1P before and after Tomotherapy have potential as diagnostic and prognostic markers for human PCa.

Radiation affects not only its direct targeted cells but also non-irradiated neighbors. This is evidenced by radiation-induced bystander effect (RIBE) that cells that were not exposed to radiation exhibit effects as a result of intercellular communication. RIBE can also lead to biological changes in bystander cells and tissues, including chromosomal rearrangement, genomic instability, DNA damage, gene expression alteration, and apoptosis [5, 10], Sphingosine-1-phosphate, play important roles as second messengers regulating biologic processes, such as cell growth, differentiation, migration, and apoptosis. Our data indicate a direct involvement of S1P in the radiation-induced bystander effect.

Conclusions

1. The levels of normal tissue S1P are significantly higher as compared with PCa. There is a significant correlation between plasma PSA and tumor tissue S1P in PCa.

2. S1P is synthesized in the tumor tissue of prostate cancer 2-fold less than in the surrounding tumor tissue. After radiation therapy, its level in the prostate tumor increases 3-fold, and in the tissue surrounding the tumor 1.5-fold, which indicates the development of the radiation-induced bystander effect.

3. Our data provide the first evidence that tumor tissue S1P is a significant prognostic marker for PCa mortality.

References

1. Komarevtseva IO, Chebotarova AA. Vplyv zastosuvannya apoptoz-indukovanykh mezenkhimalnykh stovburovykh klityn na riven fragmentatsiyi DNK i aktyvnist systemy sfingozynu v umovakh eksperymentalnoho modelyuvannya patolohichnoho protsesu. Medychna ta klinichna khimiya. 2016. 18(1): 19–23.

2. Agrawal R, Dey A, Datta S. Pattern of Radiotherapy Treatment in Low-Risk, Intermediate-Risk, and High-Risk Prostate Cancer Patients: Analysis of National Cancer Database. *Cancers (Basel)*. 2022; 14(22). doi:10.3390/cancers14225503

3. Cheng JC, Bai A, Beckham TH. Radiation-induced acid ceramidase confers prostate cancer resistance and tumor relapse. *J Clin Invest*. 2013;123(10):4344–4358. doi:10.1172/JCI64791

4. Cozzi S, Ruggieri MP, Alì E. Moderately Hypofractionated Helical Tomotherapy for Prostate Cancer: Ten-year Experience of a Mono-institutional Series of 415 Patients. *In Vivo*. 2023;37(2):777–785. doi:10.21873/invivo.13141

5. Hara D, Tao W, Schmidt RM. Boosted Radiation Bystander Effect of PSMA-Targeted Gold Nanoparticles in Prostate Cancer Radiosensitization. *Nanomaterials*. 2022;12(24). doi:10.3390/nano12244440

6. Janneh AH, Kassir MF, Dwyer CJ, Chakraborty P, Pierce JS, Flume PA, et al. Alterations of lipid metabolism provide serologic biomarkers for the detection of asymptomatic versus symptomatic COVID-19 patients. *Sci. Rep.* 2021;11:14232. doi: 10.1038/s41598-021-93857-7.

7. Janneh AH and Ogretmen B. Targeting Sphingolipid Metabolism as a Therapeutic Strategy in Cancer Treatment. *Cancers (Basel)*. 2022 May; 14(9): 2183. doi: 10.3390/cancers14092183
8. Moradi S, Hashemi B, Bakhshandeh M, Banaei A, Mofid B. Introducing new plan evaluation indices for prostate dose painting IMRT plans based on apparent diffusion coefficient images. *Radiat Oncol*. 2022;17(1). doi:10.1186/s13014-022-02163-7
9. Nagahashi M, Yamada A, Miyazaki H, Allegood JC, Tsuchida J, Aoyagi T, et. al. Interstitial Fluid Sphingosine-1-Phosphate in Murine Mammary Gland and Cancer and Human Breast Tissue and Cancer Determined by Novel Methods. J Mammary Gland Biol Neoplasia. 2016 Jun; 21(1-2): 9–17. doi: 10.1007/s10911-016-9354-7
10. Ni J, Bucci J, Malouf D, Knox M, Graham P, Li Y. Exosomes in Cancer Radioresistance. *Front Oncol*. 2019;9. doi:10.3389/fonc.2019.00869
11. Nunes J, Naymark M, Sauer L. Circulating sphingosine-1-phosphate and erythrocyte sphingosine kinase-1 activity as novel biomarkers for early prostate cancer detection. *Br J Cancer*. 2012;106(5):909-915. doi:10.1038/bjc.2012.14
12. Pustovoit GL, Sarychev, LP, Savchenko RB, Sarychev YV, Ustenko RI, Sukhomlin SA. Anticholinergic burden in aging patients and its role in the development of bladder decompensation. World of Medicine and Biology. 2022; 81(3): 138–142.
13. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin*. 2021;71:209–249. doi: 10.3322/caac.21660.
14. Wu Y, Liu Y, Gulbins E, Grassmé H. The Anti-Infectious Role of Sphingosine in Microbial Diseases. *Cells*. 2021;10:1105. doi: 10.3390/cells10051105.
15. Zhang F, Wang L, Li Y. Optimizing mesoderm progenitor selection and three-dimensional microniche culture allows highly efficient endothelial differentiation and ischemic tissue repair from human pluripotent stem cells. *Stem Cell Res Ther*. 2017;8(1):1-15. doi:10.1186/s13287-016-0455-4

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CLINICAL AND PATHOPHYSIOLOGICAL SUBSTANTIATION OF THE MUTUAL AGGRAVATION SYNDROME IN COMBINED COMBAT THERMOMECHANICAL INJURY

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There was a comparative integrated clinical examination of 93 persons with combined combat thermomechanical injuries, 87 persons with isolated extremity injuries involving bone fractures and 65 persons with isolated burn injuries. The said examination covered the recording of integral body rheography, study of coagulation tests results, biochemical, immunological blood indicators at admission on 1–3 and 5–7 days after the injury. The authors believe that only persons with extremely severe combined combat thermomechanical injuries, when there are two or more isolated injuries (wounds and burns), experience severe homeostasis disorders, which is demonstrated by the mutual aggravation syndrome with central hemodynamics as the leading link in its pathogenesis.

Key words: mutual aggravation syndrome, combined combat thermomechanical injuries, shock.

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КЛІНІКО-ПАТОФІЗІОЛОГІЧНЕ ОБҐРУНТУВАННЯ СИНДРОМУ ВЗАЄМНОГО ОБТЯЖЕННЯ ПРИ КОМБІНОВАНІЙ БОЙОВІЙ ТЕРМОМЕХАНІЧНІЙ ТРАВМІ

У 93 постраждалого з комбінованою термомеханічною бойовою травмою, у 87 – із ізольованим пораненням кінцівок з переломом кісток та у 65 – із ізольованою опіковою травмою проведено порівняльне комплексне клінічне обстеження, що включає реєстрацію інтегральної реографії тіла, вивчення коагулограми, біохімічних, імунологічних показників крові на час вступу, на 1–3, 5–7 добу після травми. Автори вважають, що тільки у постраждалих з вкрай тяжкою комбінованою термомеханічною бойовою травмою, коли є два і більше ізольовані ушкодження (поранення та опіковий компонент) розвиваються виражені порушення гомеостазу, що знаходить відображення у «синдромі взаємного обтяження» в патогенезі якого, провідною ланкою є центральна гемодинаміка.

Ключові слова: синдром взаємного обтяження, комбінована бойова термомеханічна травма, шок.

The study is a fragment of the research project "Development of modern methods of diagnostics and treatment of purulent – septic complications of combat surgical trauma", state registration No. 0120U101834

There was a comparative integrated clinical examination of 93 persons with combined combat thermomechanical injuries, 87 persons with isolated extremity injuries involving bone fractures and 65 persons with isolated burn injuries. The said examination covered the recording of integral body rheography, study of coagulation tests results, biochemical, immunological blood indicators at admission on 1–3 and 5–7 days after the injury.