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RADIATION EFFECTS ON MORPHOFUNCTIONAL STATE OF THE GASTROINTESTINAL TRACT (LITERATURE REVIEW)

Long–term radiation pathology of the digestive tract may develop from both the external radiation sources and radionuclides incorporation for which the gastrointestinal tract is one of the most accessible routes of entrance in organism. Numerous studies have confirmed that ionizing radiation damages the intestinal villi, causes irreversible changes in the form of atrophy, epithelial metaplasia, and formation of neoplastic processes. In residents affected regions exposed to effect of nuclear weapons tests and in survivors after atomic bombing in Hiroshima and Nagasaki were observed the damage to the gastrointestinal tract manifesting by formation of non–specific inflammatory changes. Since the most sensitive to radiation has the intestinal epithelium, the most frequently encountered is radiation enteritis.
Keywords: *ionizing radiation, gastrointestinal syndrome, intestinal epithelium, radiation enteritis*

Introduction.
It is known that accidental high–dose radiation exposure induces a series of injury levels in multiple organs [1]. Radiation toxicity is associated with the stimulation of acute radiation syndromes involving the gastrointestinal tract [2], which has the second highest sensitivity to radiation after bone marrow [3, 4]. As the literary sources, the highly radiosensitive intestine is an important dose–limitative organ in both total body and abdominopelvic radiation [5]. Most of studies regarding the fast neutron effect have focused at intestinal changes [6, 7]. One of main neutron–activated radionuclides promoting to the γ– and β–external dose of the atomic bomb survivors were ^{56}Mn and ^{60}Co [8], among which ^{56}Mn became one of the dominant neutron caused by β–irradiator during first few hours following A–bomb explosion in Japanese cities [9, 10]. It was determined the origin of nuclear dust and to explored the correlation between nuclear dust expression and clinicopathologic parameters of colitis [11]. Currently, particular interest is a comparative characteristic morphological and physiological changes in the immunocompetency organs of persons exposed to ^{56}Mn and ^{60}Co [12]. It was previously reported the internal dose estimates in organs of ^{56}Mn–exposed rats. The highest doses were recorded in the small intestine [13].
The research purpose: identification of differences between the nature of the structural changes in the gastrointestinal organs at different levels and types of radiation exposure.
Materials and methods.
To achieve this purpose we have searched and analysis of scientific publications. All received working to the review formation has been indexed in the databases PubMed, Medline, E–library, Cyberleninka using «Google Scholar» scientific search engine. The following search filters has been presented before the start of the search: studies carried out on experimental animals published in English, Japanese and Russian languages, as well as full versions of papers with legibly formulated and statistically proven conclusions. The key points of search requests were submitted to the following elements: «ionizing radiation», «gastrointestinal syndrome», «intestinal epithelium», «radiation enteritis».
Exclusion criteria included a review of publications became summary reports, newspaper articles and personal notifications. There were found 1150 literary sources of which were for analysis selected 82 papers.
Results and discussion.
According to several authors, acute radiation intestinal damage triggers apoptosis of intestinal crypt, which observed within a period of some hours in rodents [14, 15]. Apoptosis is a major pathogenic peculiarity of radiation–induced small intestinal mucosal injury, and its degree reflects the mucositis degree [16]. Dysfunction or death of intestinal epithelial cells caused by massive apoptosis after radiation influence is considered as dangerous component in the pathogenesis of gastrointestinal syndrome [17], that is the primary radiotherapy–associated complication in clinical use and efficacy of ionizing radiation for treating abdominal and pelvic cancers [18]. Thus, cell death after radiation can be caused by apoptosis and by mitotic catastrophe [19]. However, the underlying molecular mechanism of radiation–induced intestinal injury is still not well understood. Although some authors believe that intestinal stem cells, almost always located in crypts are a crucial factor in the process [20]. However, their precise location and properties have been disputed in the absence of a definitive molecular marker. Various studies indicated that cells at position +4 (label–retaining cell) in the intestinal crypt above Paneth cells are putative stem cells [21, 22]. Evidence obtained using genetic modification technology has convincingly shown that intestinal stem cells are columnar cells at the crypt base intermingling with Paneth cells [23]. Most authors suggested that radiation–induced apoptosis of putative intestinal stem cells, which reside at the +4 position from the crypt bottom is the primary factor initiating gastrointestinal syndrome, whereas others believe that the cells initially targeted by radiation are vascular endothelial cells in the crypt–villus axis, and it then switches to the intestinal stem cells [24, 25, 26, 27]. Given that intestinal stem cell apoptosis is the main factor involved in the initiation and development of radiation–induced gastrointestinal syndrome, radiation oncologists and medical researchers have been seeking radioprotective agents for the intestine that would help to limit intestinal cell death and facilitate intestinal crypt reproduction. Several protective substances that minimize radiation–induced intestinal apoptosis have been known for decades [28]. In the initiation of radiation–induced gastrointestinal syndrome intestinal crypt stem cell apoptosis dominant over villus vascular endothelial cell apoptosis [29]. Previous studies implicated vascular endothelial cell apoptosis in the development of gastrointestinal syndrome [25]. Numerous studies have confirmed that multifunctional adaptor proteins have indispensable roles as adaptors in apoptosis–associated signal transduction [30, 31, 32, 33, 34].

Radiation injury to stromal cells, smooth muscle and endothelium in combination with progressive, obliterative vasculitis leads to the bowel wall necrosis [35]. The small intestine is among the most quickly self–renewing tissues in adult mammals [36]. It is known that mesenchymal cells neighbouring crypts, such as subepithelial myofibroblasts acts as niche cells to support small intestinal stem cells [37, 38, 39], possessing by high regenerative ability upon tissue injury [40]. Radiation–induced cellular damage is attributed by reactive oxygen species (ROS) [41], which inducing oxidative damage, including lipid peroxidation [42, 43, 44, 45]. ROS–dependent oxidative stress, triggers DNA damage and inflammation in the small intestine [46]. Inflammatory process occurs continuously through factors involved in tissue injury or recovery. Initiated by ROS markers of lipid peroxidation were mainly detected in the muscularis externa, serosa of intestine and at the edges of villi [47], where are differentiated, specialized cells, including absorptive enterocytes, mucous–secreting goblet cells, and hormone–secreting enteroendocrine cells [36]. Thus, initiation, progression and chronicity of radiation–induced intestine injury can be caused by disorder of and molecular mechanisms and metabolic process, which form an compounded response [48, 49, 50, 51].

In the irradiated intestinal tissues observed enlargement of goblet cells, epithelial desquamation and prominent edema in lamina propria [52]. Moreover, it was revealed damage to endothelial cells and microvessels [53], a rupture in the cellular cycle with subsequent villous atrophy [35], decrease in villous height and quantity of them; hyperemia and infiltration of the lamina propria by activated inflammatory cells [54, 55, 56]. Histological studies conducted by O. Algin (2011) showed also existence of ulcerations in the intestinal mucosa with mononuclear polymorphonuclear leukocyte infiltration, formation of telangiectatic vessel and serosal adhesion, intestinal wall necrosis. Large necrosis was present in the terminal ileum serosa and in the surrounding adipose tissue. Furthermore, it were detected associated fibrinous exudates, granulation characterized by capillary hypervascularity. Data morphologic findings were consistent with radiation enteritis (RE) of the small intestine [57].

By the recommendations of authors, the prevalent term «radiation enteritis» is a misnomer, and the terms «radiation enteropathy» or «radiation mucositis» are used as a more exact definition of the pathologic process [58]. Increased defective vessels chemotaxis and thrombogenesis are the main mechanisms promoting to radiation enteropathy [59]. In contradistinction to gastrointestinal syndrome models, the model of radiation enteropathy demonstrates exploration of the enteritis progression and radiation–induced late effects [60]. Extensive data suggest that RE occurs as a result of the chronic inflammatory interaction [61]. The enteritis is most frequent side effect of radiotherapy at treatment of gastrointestinal pathology [62, 63] and defined as inflammation and damage of the small intestinal mucosa after short exposure to radiation at the abdomen and pelvis [64], which leads to decreased life quality through indigestion. In the small intestine, the tolerance dose, defined as the highest radiation dose that some organs can tolerate, acts as a limiting factor being a predictor for radiation–induced enteritis [65]. Due to the organs sensitivity to radiation, volume of irradiated tissue, and some patient feature, RE may presents in the form of acute or a chronic syndrome that should consider attending physicians [66, 67]. Acute radiation enteritis (ARE) is manifested by suddenly developing gastrointestinal symptoms directly after the radiotherapy, which undergo regression within several months after treatment completion. Whereas the clinical diagnosis of ARE is not difficult, the diagnosis and management of chronic radiation enteritis (CRE) is considerably more difficult [68]. Affected volume of small intestine and total radiation dose are the most significant risks factors of acute and late toxicity. Acute inflammation usually transformed into chronic status with arteriolar endarteritis. This progressive vasculitis induces intestinal ischemia that leads to mucosal friability, neovascularization and exaggerated submucosal fibrosis [69]. CRE can be a progression from a late formation, which directly associated to frequency of dose fractionation and field size of radiation [70, 71]. CRE also characterised by the intestinal wall thickening, ulceration and fibrotic process, leading to intestinal stricture, fistula and even perforation. Due to insufficient intestinal mucosa for nutrition absorption, most CRE patients suffer from mild, moderate or severe malnutrition [72]. Clinical manifestations of CRE include weight loss, abdominal pain, malabsorption, stricture, intestinal obstruction [73], diarrhea and rectal bleeding [74, 75]. Pathophysiological substrate of clinical manifestations of digestive diseases are primarily inflammatory mechanisms [76]. It should be noted that radiation toxicity to the gastrointestinal tract can be reduced by physically shift the radiation dose away from the normal tissues or by means of modulation the cellular and tissue response to ionising radiation [77]. Reducing the number of lymphoid cells in the small intestinal lymph nodes extends the adaptive capacity of the organism helping increase the organism resistance to the radiation factor [78, 79, 80, 81].

Conclusion.

Summing up, presented by us the information about assessment of radiation effect on the intestine on the grounds of foreign and domestic literature shows that the majority of the leading trends in the field of radiobiology and radiation medicine research there is no consensus. In this regard, for morphologists are necessary the continuation of study the γ– and neutron radiation effects on the gastrointestinal organs, which will help to develop diagnostic criteria to assess the effect of the radiation factor [82].

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АСҚАЗАН–ІШЕК ЖОЛДАРЫНЫҢ МОРФОФУНКЦИОНАЛДЫҚ ЖАҒДАЙЫНА РАДИАЦИЯНЫҢ ӘСЕРІ (ӘДЕБИ ШОЛУ)

Түйін: Асқорыту жолдарының ұзақ мерзімнен кейін туындайтын радиациялық патологиясы радиацияның сыртқы қайнар көзі әсерінен де, радионуклидтер инкорпорациясы әсерінен де дамиды, себебі олардың организмге енуі асқазан–ішек жолдары арқылы жүзеге асады. Көптеген зерттеулер мәліметтеріне сай иондаушы радиацияның ішек талшықтарын зақымдайтыны, сонымен қатар атрофия мен эпителиалды метаплазия жүзіндегі қайтымсыз өзгерістердің және ісіктік үрдістердің дамуына себепші болатыны күмән тудырмайды. Ядролық қаруларды сынақтан өткізген аймақтарда зардап шеккен тұрғындардың және Хиросима мен Нагасакида атом бомбалауынан кейін тірі қалған жандардардың асқазан–ішек жолдары бүліністері арнайыланбаған қабынулық өзгерістер дамуымен сипатталады. Сәуле әсеріне ішектік эпителийдің аса сезімтал болуына байланысты радиациялық энтерит анағұрлым жиі кездеседі.
Түйінді сөздер: иондаушы радиация, асқазан–ішек синдромы, ішектік эпителий, радиациялық энтерит

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ВЛИЯНИЕ РАДИАЦИИ НА МОРФОФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ЖЕЛУДОЧНО–КИШЕЧНОГО ТРАКТА (ОБЗОР ЛИТЕРАТУРЫ)

Резюме: Отдаленная радиационная патология пищеварительного тракта может развиться в результате как от воздействия внешних источников радиации, так и инкорпорации радионуклидов, для которых желудочно–кишечный тракт является одним из наиболее доступных путей поступления в организм. Многочисленными исследованиями подтверждено, что ионизирующее излучение повреждает кишечные ворсинки, вызывает необратимые изменения в виде атрофии, эпителиальной метаплазии и образование опухолевых процессов. У

пострадавших жителей регионов, подвергшихся влиянию испытаний ядерного оружия и у выживших после атомной бомбардировки в Хиросима и Нагасаки отмечались повреждения желудочно–кишечного тракта, проявляющиеся образованием неспецифических воспалительных изменений. Поскольку наибольшей чувствительностью к излучению обладает кишечный эпителий, наиболее часто встречаемым является радиационный энтерит.
Ключевые слова: ионизирующее излучение, желудочно–кишечный синдром, кишечный эпителий, радиационный энтерит