Low-Dose Radiation Therapy for COVID-19 Pneumonia: review

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The interest to low-dose radiation therapy (LDRT) of patients with pneumonia was also supported by researchers of radiation hormesis in the 21st century: an analytical review in 2013 [5] covers the results of treatment of 863 patients with pneumonia from 1905 to 1943 with positive results of 83.08 % of observations.

The concept of "radiation hormesis" (the term was proposed in 1980) suggests that ionizing radiation, being fatal for living organisms at high doses, in small doses can induce positive biological processes and have a stimulating beneficial effect on the body, which is recorded as a rise in fertility, growth, an increase in the life expectancy of various biological objects [1, 2, 6-8].

The conclusion that low-dose radiation therapy has an anticarcinogenic effect, which follows from the results of epidemiological studies, is confirmed by numerous laboratory experiments.

Thus, irradiation at a dose of 0.15 Gy inhibited the tumor growth after the injection of cancer cells into mice; irradiation at the same dose reduced the number of lung metastases of mice and rats; irradiation at a dose of 0.01 Gy reduced the frequency of neoplastic cell transformation; chronic irradiation of mice for 5 days at a daily dose of 0.01 Gy suppressed the occurrence of thyroid lymphoma in them [14].

The anticarcinogenic effect of LDRT was studied in 3 clinical trials with groups of patients with low- and highly-differentiated and intermediate forms of non-Hodgkin's lymphoma: against the background of chemotherapy, fractionated whole body irradiation of 0.10-0.15 Gy per fraction was performed for 5 weeks in total dose of 150 Gy. LDRT increased survival by 20-30% compared to non-irradiated control group during 4 years [15].

Elements of epidemiology. Analysis of the statistics of coronavirus infection dynamics in the regions of Ukraine demonstrates the region with the lowest incidence (table). It is impossible to draw unambiguous conclusions: the level of health care ? radiation hormesis ? the need of population stratification by a number of indicators ...

It is known [3, 4] that 95 % of uranium ore deposits in Ukraine are concentrated in the Kirovograd region. Kirovograd (Kropyvnytskyi) is the only city in the world where mining takes place almost under residential areas.

1945. High radioactivity was established at the mine of the Pervomaisky iron ore deposit.

1946. Uranium ores were discovered at the "Yellow River" mine.

1948 Uranium ore mining began at the Pervomaisky and Zheltorechensky deposits. Industrial mining is carried out underground.

USA [9]. 5 patients (mean age – 90, range from 64 to 94) from nursing homes were hospitalized after positive test for COVID-19. Each had radiographically verified pneumonia, required supplemental oxygen, and each had a clinical decline in mental status and an increased need for supplemental oxygen. A single treatment with low doses (1.5 Gy) of irradiation of both lungs was carried out for 10-15 minutes (from April 24 to April 28, 2020). Within 24 hours, 4 patients quickly improved breathing and returned to room air after an average of 1.5 days (range from 3 to 96 hours). 3 patients were discharged on the average after 12 days, and one was preparing for discharge. Blood tests and re-imaging confirm LDRT to the entire lung is safe for COVID-19 pneumonia.

Iran [10]. In the period from May 21, 2020 to June 24, 2020, 5 patients over 60 years (hospitalized to receive supplemental oxygen) were treated according to the **0.5 Gy al-**

Coronavirus infection by regions of Ukraine of 25.03.2021.

Region	Total infections	Deaths	Recovered
Kyiv	156603	3198	103722
Odessa	101783	1679	82439
Kharkiv	97986	1865	82767
Lviv	97440	2552	76479
Kyiv region	90260	1503	75784
Dnipropetrovs'k	86190	2265	73229
Ivano-Frankivsk	77395	1622	59463
Zaporizhia	75880	1351	68457
Chernivtsi	67545	1292	48881
Zhytomyr	67367	1099	49581
Khmelnits'k	59639	1072	49019
Donetsk	55455	1229	46624
Sumy	55403	780	48739
Rivne	55256	716	50058
Cherkasy	54842	725	48707
Vinnitsa	53866	941	33458
Poltava	52568	1108	44964
Zakarpattia	52234	1237	38469
Ternopil	51495	719	43378
Mykolaiv	49761	973	41311
Volynskaya	45054	735	39935
Chernihiv	40147	832	32939
Kherson	23356	689	21054
Luhans'k	16662	506	14734
Kirovograd	12388	447	8829
Total	1596575	31135	1283020

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gorithm + national protocol for the treatment of COVID-19.

Basic vital indicators (blood oxygenation and body temperature) and laboratory data (interleukin-6, C-reactive peptide) were recorded before and after irradiation for 5-7 days. Clinical and paraclinical parameters in 4 of 5 patients (1 patient died on day 3) improved on the first day of irradiation. The average discharge time for the remaining patients was 6 days. No acute radiation-induced toxicity has been registered. Thus, with a response rate of 80 %, ir-

radiation of the whole lung in a single fraction of 0.5 Gy has demonstrated encouraging results in oxygen-dependent patients with COVID-19 pneumonia.

India [11]. From June to August 2020, 10 patients with moderate to severe COVID-19 were treated with the **0.70 Gy algorithm + standard COVID-19 treatment guidelines**. In 9 patients, had complete clinical recovery, mainly within 3-7 days. One patient with arterial hypertension showed clinical deterioration and died 24 days after low-dose radiation ther-

apy. Study results (response rate 90 %) suggest the feasibility and clinical efficacy of LDRT in COVID-19 patients. This requires a randomized controlled trial to establish the clinical efficacy of LDRT for COVID-19 pneumonia.

Spain [12]. Patients: Male patient of 80 years (arterial hypertension, amputation of the right lower limb due to mixofibrosarcoma in the stage of remission), blood oxygen saturation – 80 %; Female patient of 65 years (bronchial asthma, lumbar stenosis, uterine polypectomy), blood oxygen saturation – 87 %. These patients had life expectancy of > 1 month at the time of hospitalization for COVID-19 pneumonia. Medical therapy: lopinavir/ritonavir within 7 days after admission; hydroxychloroquine, azithromycin for 3 days; piperazillin/tazobactam 5 days for a man and 14 days for a woman, prophylactic doses of low molecular weight heparins, corticosteroids and tocilizumab. Despite this pharmacotherapy, lying position and oxygen support, respiratory status and inflammatory parameters in both patients continued to deteriorate. Therefore, it was decided to administer LDRT to both patients on April 23, 2020. Rationale: the available literature on the pneumonia therapy describes the application of doses in the range of 0.50-1.25 Gy; the aggressiveness of the virus initiated the choice of a dose above 0.5 Gy; this is the minimum effective dose of the gantry rotation period of the tomotherapy device.

The total single dose was 0.8 Gy for a 3-minute session. Respiratory status improved rapidly in both patients. The man showed an improvement in oxygen saturation 2 days after LDRT and he was discharged 8 days after low-dose radiation therapy with 95 % saturation. His condition remained stable after 1 and 2 months. The woman showed a slower recovery, and a decrease in the need of oxygen support 2, 5 and 7 days after treatment. She was discharged 14 days after LDRT.

Auger therapy is a new direction in radiation therapy. It uses radionuclides that undergo electron capture and/or internal conversion, for example, ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{103}Pd , ^{111}In , ^{123}I , ^{125}I . As a result of these processes, a large number of Auger electrons with low kinetic energy (~20-500 eV) are emitted from atomic orbits. The

run length of these electrons is several nanometers, i.e. less than the size of one cell. For comparison, the run of β -particles in ^{90}Y is equivalent to the average size of 215 cells, the run of β -particles in ^{131}I is equivalent to the size of 40 cells, and the run of α -particles in ^{211}As is equivalent to the size of 3 cells. Radionuclides emitting Auger electrons are incorporated into specially selected molecules. With the help of these molecules, radionuclides are delivered to cancer cells, in close proximity to DNA. Thus, Auger electrons with their very short run make it possible to implement radiation therapy for cancer cells with minimal damage to normal tissue. CR3022 is a human antibody that binds to the SARS-CoV-2 coronavirus. The use of CR3022 as a molecular targeting radiotherapy agent was investigated. CR3022 was conjugated with ^{131}I and purified, $\rightarrow$ ^{131}I -CR3022. The CR3022 antibody was obtained with a purity of more than 98 % and a specific activity of more than 292 MBq/mg. The binding of ^{131}I -CR3022 was found to be selective and significantly decreased in the presence of unlabeled antibody (specific absorption $3.14\% \pm 0.14\%$ and specific absorption $0.10\% \pm 0.01\%$, respectively; $P < 0.0001$). Investigations confirm the potential of CR3022 as a probe with molecular target for SARS-CoV-2. The radiolabeled ^{131}I -CR3022 antibody can potentially be used for Auger radiation therapy or non-invasive imaging as an accurate and non-invasive indicator of a patient's viral load [13].

Researchers' conclusions

The studies were carried out without control groups due to extremely unusual clinical situations and poor prognosis of the disease in the absence of treatment.

LDRT – 115 years of empirical research and lack of effective and proven clinical concepts.

The carcinogenic effect of radiation therapy is the main argument of opponents.

LDRT (<100 cGy) is known for its anti-inflammatory effect, and therefore LDRT of the lungs has the potential to reduce the severity of pneumonia and reduce mortality.

LDRT deserves investigation in clinical conditions.

Conflict of interest information. The author declares no conflicts of interest related to the publication of this article.

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LOW-DOSE RADIATION THERAPY FOR COVID-19 PNEUMONIA: REVIEW

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The use of low-dose radiation therapy (LDRT) in patients with pneumonia from 1905 to 1943 provided positive results in 83.08 % of cases. Interest in LDRT is supported by researchers of radiation hormesis in the 21st century.

Attention is drawn to the dynamics of coronavirus infection in the regions of Ukraine and

the Kirovograd region with a minimum incidence. It is known that 95 % of uranium ore deposits in Ukraine are concentrated in the Kirovograd region.

The positive experience of LDRT in Iran, India, USA, Spain for the treatment of patients with COVID-19 is described.

LDRT (<100 cGy) is known to be anti-inflammatory, and therefore pulmonary LDRT has the potential to reduce the severity of pneumonia and reduce mortality. LDRT deserves a clinical study.

A new direction in radiation therapy – Auger therapy based on radiolabeled antibodies – is planned to be used as a molecular targeting radiotherapy agent directly to the SARS-CoV-2.

НИЗКОДОЗОВА ПРОМЕНЕВА ТЕРАПІЯ ПРИ COVID-19 ПНЕВМОНІЇ

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Використання низькодозової променевої терапії (НДПТ) хворих з пневмонією з 1905 р. по 1943 р. забезпечило позитивні результати в 83,08 % спостережень. Інтерес до НДПТ підтримується дослідниками радіаційного гормезису в ХХІ столітті.

Звернуто увагу на динаміку інфікування коронавірусом по областях України і на Кіровоградську область з мінімальною захворюваністю. Відомо, що в Кіровоградській області сконцентровано 95 % покладів уранових руд України.

Описано позитивний досвід використання НДПТ в Ірані, Індії, США, Іспанії для лікування хворих з COVID-19. НДПТ (<100 сГр) відома своєю протизапальною дією, і тому НДПТ легень потенційно може знизити тяж-

кість пневмонії і знизити смертність. НДПТ заслуговує вивчення в клінічних умовах.

Новий напрямок в променевої терапії – Оже терапія на основі радіомічених анти-тіл – планується використовувати в якості радіотерапевтичного засобу молекулярної націленості безпосередньо на коронавірус SARS-CoV-2.

НИЗКОДОЗОВАЯ ЛУЧЕВАЯ ТЕРАПИЯ ПРИ COVID-19 ПНЕВМОНИИ

Н.Н. Колотілов

Использование низкодозовой лучевой терапии (НДЛТ) больных с пневмонией с 1905 г. по 1943 г. обеспечило положительные результаты в 83,08 % наблюдений. Интерес к НДЛТ поддерживается исследователями радиационного гормезиса в ХХІ веке.

Обращено внимание на динамику инфицирования коронавирусом по областям Украины и на Кировоградскую область с минимальной заболеваемостью. Известно, что в Кировоградской области сконцентрировано 95% залежей урановых руд Украины.

Описан положительный опыт использования НДЛТ в Иране, Индии, США, Испании для лечения больных с COVID-19. НДЛТ (<100 сГр) известна своим противовоспалительным действием, и поэтому НДЛТ легких потенциально может снизить тяжесть пневмонии и снизить смертность. НДЛТ заслуживает изучения в клинических условиях.

Новое направление в лучевой терапии – Оже терапия на основе радиомеченных антител – планируется использовать в качестве радиотерапевтического средства молекулярной нацеленности непосредственно на коронавирус SARS-CoV-2.