THE DYNAMICS OF ELEMENT CONTENT IN PATIENTS WITH LUNG CANCER DURING RADIOTHERAPY

***N.P. Dikiy*[1]*, *Yu.V. Lyashko*[1], *E.P. Medvedeva*[1],
V.I. Borovlev[1], *V.D. Zabolotny*[1], *D.V. Medvedev*[1],
N.I. Pilipenko[2], *V.P. Starenky*[2], *E.N. Suhina*[2]**

[1] *National Science Center "Kharkov Institute of Physics and Technology", 61108, Kharkov, Ukraine*

[2] *Grigoriev Institute for Radiology, 61024, Kharkov, Ukraine*

(Received June 6, 2009)

Determination of the element contents in the biological samples (blood, serum of blood, hair) of patients with the diagnosis of lung cancer III degree is carried out during beam therapy. The method of PIXE excited by protons on the accelerator with energy 3 MeV has been used. During radiotherapy the difference in the element contents in hair of patients has not been detected. Trustworthy reduction of Fe, Cu, Mn, Ca, Sr, Rb etc is marked during treatment. The obtained results can be used as the additional test at carrying out adequate treatment in radiotherapy.

PACS: 29.30.Kw

1. INTRODUCTION

The lung cancer is the most widespread oncological disease, in particular, among males, and its incidence is above 30% [1]. The risk factors of this disease may be related to smoking, occupational activity, environmental contamination, chronic bronchitis and pneumonia. The influence of many risk factors on the tumor development and different mechanisms of microelement (ME) transport into the malignant and unaffected tissues is one of primary problems in the study of this disease. The ME content in normal organs and tissues for the most part will depend on the age, sex, mode of nutrition, geographic-and-climatic conditions and genetic factor.

Biological role of such elements as Fe, Cu, Zn, Mn, Se, Rb, Br, I, Ca etc in different diseases is intensively studied [2,3]. Almost all these elements are basic components of ferments and biologically active systems. All metals, except I, F and Se play important role as cofactors in enzymes. Fe in the form of heme is contained in the composition of hemoglobin, myoglobin, cytochrome and dehydrogenase. Cu is contained in a number of ferments (tyrozine, amine oxidase, cytochrome-c-oxidase, transferase etc) and the role of Cu in the vitamin B_{12} is known. Zinc is in the composition of carboxypeptide, aminopeptide etc [4]. Se, as an element-antioxidant, was detected in many tumor tissues [5]. Different concentrations of Mn are found in earlier proliferative phases. There is available information about the function of someone else essential ME in the case of oncogenesis.

The concentration of essential ME can undergo significant changes in the course of the radiotherapy and chemotherapy. In the latter case it is very important to know how these ME can be used as biological additives for cancer carriers in the course of diagnosis and prognosis. The main goal of this work is to study the element contents of the blood serum and hairs of lung cancer patients in the course of radiotherapy.

2. MATERIALS AND METHODS

The method of characteristic X-ray (PIXE) excited by protons was used to determine the ME content in the biological samples (blood, blood serum, hair) being investigated [6].

The main principle of the method applied is the X-ray excitation in the samples under the action of accelerator protons. The PIXE spectrum from the target permits to obtain qualitative information on the ME content in the samples.

The measurements were carried at accelerator PG-5 with energy 3 MeV of NSC KIPT. The 2.5 MeV proton beam collimated to 3 mm was impinging on the target at an angle of 45^o. The intensity of the beam impinging on the Faraday cap was measured by the current integrator. PIXE from the target, after passing through the 10 μm window of thin aluminium-metallized Mylar, was measured by means of the Si(Li)-detector with a resolution of 280 eV on the line of 6.4 keV and 30 mm^2 area placed in the vacuum system. The absolute limit of detecting was achieved 10^{-12} g, and relative - 0,1 μg/g. The absolute values of ME concentrations were determined by the standard sample-preparation method and by introducing the internal standard (yttrium).

Mathematical spectrum treatment was performed by the SLED program. The papers presents the re-

*Corresponding author E-mail address: ndikiy@kipt.kharkov.ua

sults of survey for 32 lung cancer patients (stage III) undergoing the course of radiotherapy by the radical program in the department of distance radio- and complex therapy of the Kharkov Research Institute for Medical Radiology. In the group of examined patients were males at the age from 45 to 65 years. For 71% of these patients the diagnosis was confirmed morphologically and corresponded to the following diseases: adenocarcinoma of a different degree of differentiation 6 (26%), epidermoid carcinoma 17 (74%), in the rest 9 cases the cancer was diagnosed without histological structure specification.

The patients were irradiatied at the linear electron accelerator LUEV-15M1 under conditions of bremsstrahlung with a limiting quantum energy of 15 MeV. The treatment was carried out by the two-pole method - anterior and posterior fields on the lesion side or with the capture of an opposite root of lung. The total focal dose was varying from 55 to 65 Gy depending on the morphological structure and the degree of tumor differentiation and was reached during 5-7 weeks by the splitting method.

The control group comprised 20 donors. Investigations of blood serum- and hair samples were repeated three times: before the treatment, in the middle and after the termination of the first step of the radical irradiation program, respectively.

Liquid blood, blood serum samples were dried in the drying chamber at a temperature of $40^\circ C$ until the sample weight was unchangeable during 3 days, then its were minced in the agate mortar and were applied by thin layers ($1...20\,mg/cm^2$) onto the substrate of spectroscopically pure graphite with a carrier of $50\,mg/cm^2$ thickness. In one of samples added were the reference elements, for example, yttrium and elements-additives (from 3 to 5) of a given concentration minced in the agate mortar. The hair samples were prepared according to the IAEA recommendations [7]. At the front of the detector an aluminium filter of $15\,\mu m$ thickness was placed. The proton dose was $3\,\mu C$ and the intensity did not exceed $15\,nA/cm^2$. The detection limit was $1\,\mu g/g$ of dried mass.

3. RESULTS AND DISCUSSION

The determination of the ME content in the blood serum and hairs was carried out for each of samples in the group of patients and donors. In Fig.1 shown is the original spectrum of the element content in the hairs of patients with lung cancer in stage III (patient P.) before the treatment. There were not observed appreciable changes in the investigated samples in comparison with the norm. In the course of radiotherapy there were not observed any significant distinctions in the content of elements in the patient hairs. However, during the investigation the Pb concentration in the hairs of all patients was $3...10\,\mu g/g$ that exceeded the mean Pb concentration relative to the control group. The samples of some patients contained uncertain increased selenium amount.

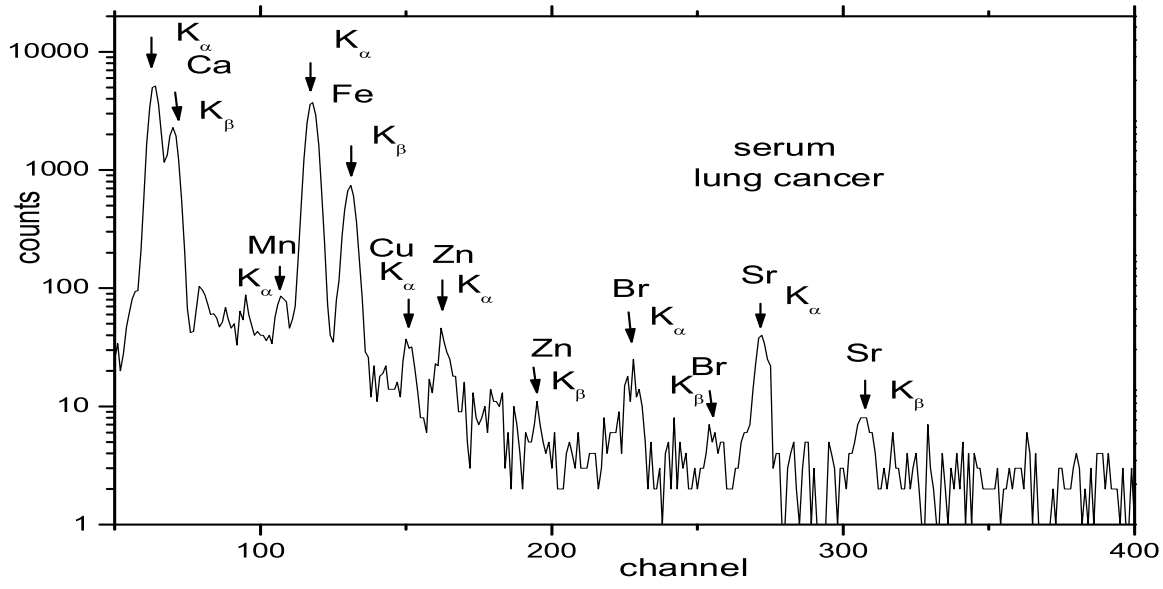

Fig.1. *Spectrum of X-ray radiation from the blood serum of patients with lung cancer (patient O)*

According to the data, obtained before the treatment, the concentration of such elements as manganese, strontium, rubidium etc in the blood serum of patients is higher that of donors. The dynamics of investigations on the elemental composition in the blood serum during the course of radiotherapy has demonstrated a certain decrease of almost all determined elements as compared to the content of these

elements before the treatment. Fig.2a and Fig.2b show that such elements as iron, copper, calcium, strontium undergo the most significant changes. It is common knowledge that iron is a metal of a variable valence participating in the process of free radical peroxidation (FRPO) in the stage of hydrogen peroxide decomposition with formation of an active radical leading to the chain branching [8,9].

Calcium ions are the FRPO regulators capable to replace iron and to transform it in the active form.

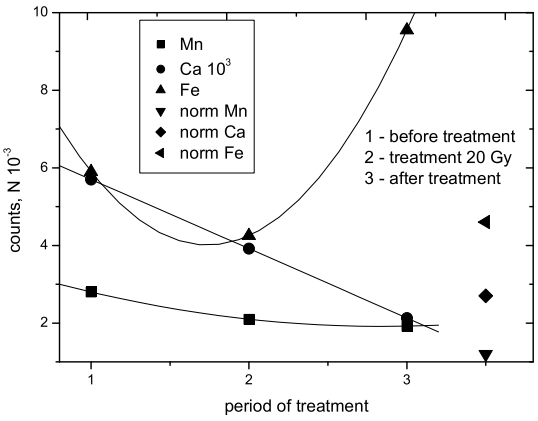

Fig.2a. *Content of elements in the blood of patients with lung cancer depending on the treatment period*

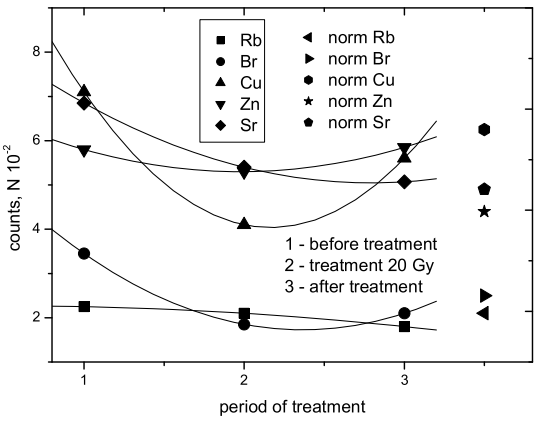

Fig.2.b. *Content of elements in the blood of patients with lung cancer depending on the treatment period*

he decrease in the concentration of manganese and copper is obviously related with the reducing activity of such ferments as superoxide dismutase and ceruloplasmin that evidences on the decrease of the reserve in this system and on the probability of inclusion of other regulatory factors.

The presence of bromide in the blood serum and character of its changing in the course of radiotherapy may be related with the iatrogenic effect of patient treatment.

It should pay attention to the behavior of such an element as zinc, which in the dynamics of investigations almost does not undergo any changes. It is in good agreement with the literature data confirming that the zinc concentration in the blood serum is one of the most stable characteristics [10]. Zinc is the element - FRPO inhibitor stabilizing the permeability of cellular and intercellular membranes. This element comes into competitive interrelations with calcium and realizes its antagonism at a level of ferments. So, by analyzing the results of investigation on the elemental composition of the blood serum of patients with lung cancer, it could be noted that some of revealed changes reflect adequately the peculiarities of organism reaction on the radiotherapy action. The performed correlation analysis between the element content values in the patient blood depending on the treatment period did not revealed significant changes, although the certain simplification of correlation bonds took place. It has been established that there are strong correlations between the elements determined before the treatment and these determined in the middle of course of treatment (correlation coefficient CC=0.88). The correlation bonds were also significant (CC=0.52)) for the element contents in the middle and in the termination of course of treatment. Weakening of the correlation structure (CC=0.44) is observed for the element content after the termination of course of treatment with the same value as in the beginning of the course of therapy. The loss of significant bonds between zinc and boron (CC=0.45), and, also, between rubidium and zinc (CC=0.31) was observed. In conclusion, it should be noted that the use of the multiple-element high-sensitive PIXE method for determining the element content in samples of patients with lung cancer (stage III) is of a particular interest for the study of the dynamics of changes in the organism's microelement status. The results obtained can be used when the adequate corrective therapy is assigned in the process of radiation exposure including Ca-antagonists, copper-containing drugs and antioxidants.

4. CONCLUSIONS

1. The nuclear method PIXE was used for determining the ME content in the hair, blood and blood serum of patients with lung cancer (stage III) during the radical course of radiotherapy. Such elements as Fe, Mn, Cu, Zn, Ca, Br, Sr, Rb were determined.

2. In the course of radiotherapy any significant distinctions in the element content in the patient hairs relative to the norm were not observed.

3. In the blood of patients with lung cancer before the radiotherapy application the concentration of such elements as manganese, calcium, strontium, rubidium was reliably higher than that of the donor. The radiotherapy effect resulted in the significant decrease of all the elements being investigated.

4. The obtained results on the ME content in the radiotherapy dynamics can be used for the course of corrective therapy.

References

1. A. Jemal, A. Thomas, T. Murray, M. Thun. Cancer statistics // *CA Cancer J. Clin. 2002*, v.52, p.23-47.

2. K. M. Schwatz Role of trace elements in cancer //*Cancer research.* 1975, v.35, p.3481-3487.

3. A. Kubala-Kukus, J. Braziewicz, D. Banas, U. Majewska, S. Gozdz, A. Urbaniak Trace element load and normal lung tissue // *Nucl. Instr. Meth. in Phys. Res. 1999*, v.B150, p.193-199.

4. M. Chvapil. New aspects in the biological role of Zinc: A Stabilizer of Macromolecules and Biological Membranes // *Life Sci. 1973*, v.13, p.1041-1049.

5. H. Zhuo, A.H. Smith, C. Steinmaus. Selenium and Lung Cancer: a Quantitative Analysis of Heterogeneity in the Current Epidemiological Literature // *Canc. Epidem. Biomar. Prev. 2004*, v.13(5), p.1-19.

6. N.P. Dikiy, E.P. Medvedeva, N.A. Shlyahov, et al. *Physicaly-analytical complex in medicine. Nuclear-physical methods. Statistical treatment. Computer diagnostics:* Preprint. KIPT, 94-13, 1994, 17p. (in Russian).

7. *Reference Methods for Marine Pollution Studies*, Vienna, IAEA-MEL, 1997, N46, 193p.

8. G.A.Babenko, Y.I. Gonskiy, I.M. Antonyuk, et al. About a role of metals in process free radical oxidations in tissues of an organism according to spontaneous and induced chemiluminescence //*Biochemiluminescence, 1983.* M.: "Nauka", p.164-179.(in Russian).

9. V.C. Shapot, V.P. Shelepov About interaction of starting mechanisms of violation of a homeostasis in a tumoral organism // *Arhiv Pathologies. 1983*, v.8, p.3-12(in Russian).

10. V.M. Karpinsky Syndrome of deficiency of zinc //*Vopr. Pitaniya. 1980*, v.1, p.10-18 (in Russian).

ДИНАМИКА СОДЕРЖАНИЯ ЭЛЕМЕНТОВ У БОЛЬНЫХ РАКОМ ЛЕГКОГО В ПРОЦЕССЕ ЛУЧЕВОЙ ТЕРАПИИ

Н.П. Дикий, Ю.В. Ляшко, Е.П. Медведева, В.И. Боровлев, В.Д. Заболотный, Д.В. Медведев, Н.И. Пилипенко, В.П. Старенький, Е.Н. Сухина

Проведено определение содержания микроэлементов в биологических образцах (кровь, сыворотка крови, волосы) пациентов с диагнозом рака легкого III степени в процессе лучевой терапии. Использован метод характеристического рентгеновского излучения, возбуждаемого протонами на ускорителе с энергией 3 МэВ. В течение радиотерапии отличий в содержании элементов в волосах пациентов обнаружено не было. В процессе лечения достоверно обнаружено уменьшение Fe, Cu, Mn, Ca, Sr, Rb и т.д. в крови и сыворотке крови. Полученные результаты могут быть использованы в качестве дополнительного теста при проведении адекватной терапии в курсе лучевого лечения.

ДИНАМІКА ВМІСТУ ЕЛЕМЕНТІВ У ХВОРИХ РАКОМ ЛЕГЕНІ В ПРОЦЕСІ ПРОМЕНЕВОЇ ТЕРАПІЇ

М.П. Дикий, Ю.В. Ляшко, О.П. Медведева, В.І. Боровльов, В.Д. Заболотний, Д.В. Медведев, М.І. Пилипенко, В.П. Старенький, О.М. Сухіна

Проведено визначення вмісту мікроелементів в біологічних зразках (кров, сироватка крові, волосся) пацієнтів з діагнозом раку легені III ступеня в процесі променевої терапії. Використовувався метод характеристичного рентгенівського випромінювання, яке збуджувалось протонами прискорювача з енергією 3 МеВ. Протягом радіотерапії відмінностей у вмісті елементів у волоссях пацієнтів виявлено не було. У процесі лікування вірогідно виявлене зменшення Fe, Cu, Mn, Ca, Sr, Rb і т.д. в крові і сироватці крові. Отримані результати можуть бути використані як додатковий тест при проведенні адекватної терапії в курсі променевого лікування.