

## Cardioncology in Russia: Start-Off and Prospects

*Prof. Marina F. Ballyuzek, MD PhD<sup>1, 2, 3</sup>, Maria V. Mashkova, MD<sup>4</sup>*

*<sup>1</sup> Medical Director of St. Petersburg Hospital of Russian Academy of Sciences*

*<sup>2</sup> Head of Cardiology Department, St. Petersburg Hospital of Russian Academy of Sciences*

*<sup>3</sup> Therapy Department, St. Petersburg State University*

*<sup>4</sup> St. Petersburg Hospital of Russian Academy of Sciences*



### ABSTRACT

The progress in improving the survival of cancer patients in Russia, as well as throughout the world, means that in the next years it is going to be an increase in the number of disabled people who has achieved remission, or who faces the consequences of high-dose polychemotherapy and/or radiotherapy between courses of cancer treatment. Until recently, the two main socially significant medical problems in Russia, cancer and cardiac, have been rarely united into one. Publications on this topic appeared only in specialized cancer journals and were unknown by a wide range of cardiologists and internists, therefore the involvement of these specialists in the study of theoretical and practical aspects of the management of patients with malignant tumors was limited. Creation of the International Society of Cardioncology (ICOS) contributed to the development of an interest in this interdisciplinary field of modern medicine.

However, even today cardiac problems of cancer patients in Russia mostly are limited to the cardiotoxicity studying, but, according to the position of the authors a great attention should be paid to the systemic reactions, including cardiovascular reactions of the organism to the tumor, as well as to the therapeutic issues and cardiac rehabilitation of cancer patients.

**KEY WORDS:** cardioncology in Russia, cardiotoxicity, systemic cardiovascular reactions to the tumor, cardiac rehabilitation of cancer patients

According to the Russian Federal State Statistics Service (*Rosstat*), in 2012, every minute a patient was diagnosed with cancer in the country, while over 3.0 million people were registered with cancer care facilities [1]. According to statistics, during the last 10 years the number of cancer patients in Russia has grown by 25.5%, and unless the situation changes their numbers will increase by another 15–20% [2]. Most dispiriting is the fact that in 60% of the cases the illness is diagnosed only at the III or IV stages [1]. Grievous statistics also comes from the International Agency for Research on Cancer (GLOBOCAN 2008, IARC), which says that in oncology-related mortality rates, Russia occupies the 5<sup>th</sup> place in the world [3].

The main part of the patient contingents include those suffering from neoplasms in mammary glands (18.2%), uterus body (7.1%), lymph and hematopoietic tissues (5.6%), colon (5.6%), neck of uterus (5.5%), ventricle (4.5%), prostate (4.5%), rectum (4.3%), thyroid gland (4.3%) and trachea, bronchi and lungs (4.1%) [1].

Of the patients that have been under observation for over 5 years, the largest proportion is made up of those with mammary tumor (20.6%), tumor of body (8.3%) or neck (7.0%) of uterus, cancer of lymph and hematopoietic tissues (5.8%), thyroid gland (5.4%), colon (5.4%), ventricle (4.7%), prostate (4.2%), kidney (4.0%), ovaries (3.5%), trachea, bronchi and lungs (3.1%) [1].

In 2012, the prevalence index of malignant tumors among children under 15 years of age was 67.6 per 100 000 children (rising to 72.3 for children aged under 17). The proportion of patients aged under 15 who had been undergoing treatment for over 5 years was 36.3% of the total number of patients treated (with 40.6% for patients under 18). In 2012, the incremental index for children under 14 was 5.5 (with 5.9 for patients under 18). Lethality rates were 3.9% and 3.8%, while lethality rates for one year were 10.8% and 10.9% for patients under 14 and those under 17, correspondingly [1].

However, the considerable increase in the prevalence of malignant tumors in Russia is not only due to the growth of the sickness rate, but also to the increased survival rate of cancer patients [1].

Obviously, oncological therapy in Russia has made considerable progress during recent years. Due to the introduction of high-tech methods, it has become possible to undertake radical treatment of many patients who would have been considered hopeless just a few years before. At the same time, such treatment often involves incapacitation of the patient following extensive organ extraction, as well as polychemical and radiation therapy. In practice, progress in increasing the survival rate of cancer patients may actually mean an increasing number of disabled people who have reached the remission stage, or people experiencing grievous consequences of high-rate polychemo- or radiation therapy in

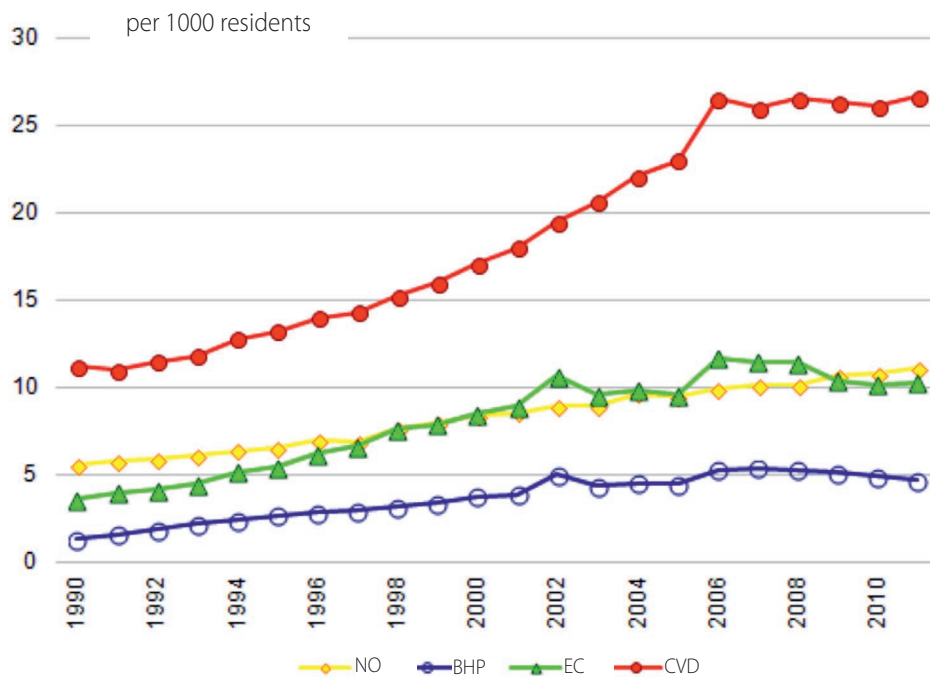
the intervals between cancer-treatment courses. All these factors increase the importance of early cancer detection, early start and ongoing treatment of the disease, as well as further observation of patients who have undergone cancer therapy.

Meanwhile, according to the Institute of Demography, the National Research University Higher School of Economics, since 1990, cardiovascular pathology has invariably been, in the overall structure, the major factor determining the death rate in Russia (Figure 1); the share of deaths caused by cardiovascular diseases amounting to 56.5% of all cases. In the overall disease pattern, this group is mostly represented by ischemic heart disease, cerebrovascular disease and hypertension [4].

However, until recently, the two medical problems of special social significance in this country, those of oncological and cardiologic morbidity and lethality, have never been considered jointly, and cardiovascular disorders in patients with malignant tumors have always been treated in the context of oncological theory and practices.

Obviously, oncologists in Russia could not help noticing such important complications characteristic of cancer treatment as acute and cumulative cardiac toxicity. One of the first publications by a group of authors from N.N. Petrov Research Institute of Oncology concerned with this subject made its appearance in 1993. This work was devoted to the prevention of doxorubicin cardiac toxicity by means of dexrazoxane (ICRF-187) during chemotherapy of wide-spread mammary cancer [5]. Later, in 1995, R.B. Orlova, one of the authors, read her doctoral thesis on this topic, where she emphasised that loss of myocardium contractility, which was caused by treatment with anthracycline antibiotics and determined by echocardiography, is an early and reliable indication of toxic cardiomyopathy. From this, it follows that the standard cardiomonitoring (physical examination, electrocardiography, chest X-ray) should be supplemented with echocardiography. Should the left ventricular ejection fraction be reduced by over 20% from the initial level, further anthracycline therapy becomes dangerous due to the high risk of causing fatal cardiac insufficiency [6]. Around the same time, several research papers on cardiotoxicity were published, which considered, in particular, its manifestations in children during hemoblastosis treatment [7]. In 2003, the same authors published data proving that 45% of children have remote cardiac complications two years after the completion of the intensive anthracycline treatment phase, when the cumulative antibiotic dose amounts to 240 mg/m<sup>2</sup>; the frequency of myocardial damage in girls (59%) was significantly higher than that in boys (41%), which allows us to consider females as a risk factor for developing remote sub-clinical cardiac toxicity in children with acute lymphoblastic leukemia [8]. The authors also emphasised

FIGURE 1.  
Prevalence of several major disease classes across the Russian Federation population, according to the number of first-time diagnosed cases, per 1000 permanent residents, 1990-2011.



NO – neoplasms; BHP – diseases of blood and hematopoietic organs; EC – diseases of endocrine system, nutritional disorders, metabolic and immunity disorders; CVD – cardiovascular diseases.

that regular cardiac status monitoring, involving standard ECG and EchoCG, should be a mandatory element of the patient observation regimen – both during and following treatment. The patients going through prolonged remission of acute lymphoblastic leukemia were recommended to have their cardiac status checked annually as indicated above; this was in accordance with the international standards of the period and was feasible for most of the multi-field pediatric clinics. More recently, the few articles on cardiac toxicity both in children and adults that have appeared in Russian journals on cancer research were mostly reviews rather than discussions of new results [9–13].

In 2012, a group of authors from Tomsk Cancer Research Institute, RAMC, published their own revealing data on the complex assessment of anthracycline cardiac toxicity using radionuclide methods of cardiac research involving ECG-synchronised myocardial perfusion tomoscintigraphy and balanced radionuclide ventriculography. Based on these diagnostic methods, the effect of anticancer drugs (mainly doxorubicine, an anthracycline antibiotic) on myocardial perfusion and function was studied [14], and the criteria were developed for acute cardiac toxicity grading. It was established that the decline of the left ventricular ejection fraction by 10 or more percent, registered by radionuclide

methods immediately after the injection of the first doxorubicine dose, indicated that the patient could be included into the high-risk group for developing cumulative cardiac toxicity. In such cases, after the first doxorubicine administration, the patients should either be preventively transferred to an alternative chemotherapy mode, or administered preventive cardio-protective drugs. In this case, the authors chose trimethylhydrazine propionate, widely used in Russia and produced by AO GRINDEX in Latvia, which was recommended for cytoprotective therapy. As seen from above, the papers were published in highly specialised journals on cancer research, remaining unknown to cardiologists and physiologists at large, therefore participation of the latter experts in the research on theoretical and practical aspects of treating patients with malignant tumors was limited. Moreover, even today doctors in all fields are in a way “dependent” on cancer diagnosis, which results in the wide-spread, but mistaken opinion that “cancer patients should only be treated by oncologists”. Moreover, until recently there was no wide awareness of the establishment of the International Cardioncology Society (ICOS) and its Eurasian department in 2009, which is mainly aimed at bringing together scientific and practical knowledge of cardiologists and oncologists. Notably, today the term “cardioncology”, accor-

ding to Russian Wikipedia, means “a medical speciality [...] at the interface between oncology and cardiology, which studies cardiac tumors, their aetiology and pathogenesis, methods of their prevention, diagnostics and treatment. In particular, cardioncology deals with cardiac myxoma, rhabdomyoma, lymphoma and lipoma”. This term is supported by a team of authors from the leading institution in the surgical treatment of cardiovascular diseases, Bakulev Scientific Center of Cardiovascular Surgery, who in 2003 published a monograph entitled “Cardioncology”. Based on extensive literature and their own experience, they gave a detailed clinical and diagnostic account as well as described the results of the surgical treatment of myxoma, non-malignant tumors, and primary and secondary malignant growths [15].

In Russian medical practice, it is also typical to interpret cardiac problems as seen by oncologists, so all the tasks are reduced to alleviating cardiac toxicity. Of the papers which have treated cardioncology more broadly, as a science developing on the interface between two important disciplines – oncology and cardiology – we can mention the publication by a group of authors from Novosibirsk, which is devoted to the study of cardiac vegetative nervous system dynamics in patients with non-Hodgkin’s lymphoma during chemotherapeutic treatment [16]. The authors showed that non-Hodgkin’s lymphoma had caused damage to vegetative nervous systems before chemotherapeutic treatment: every second patient had developed autonomous cardiovascular neuropathy, while every third – a reduction of heart rate variability. In the process of chemotherapeutic treatment, the changes in the cardiac vegetative nervous system were shown to be aggravated. These changes could only be observed by standard vegetative tests and calculating the cardiac rate variability index. The standard examination (ECG in 12 leads taken during 1 minute) did not provide such information. The paper stated that the damage to the cardiac vegetative nervous system was multi-factorial, associated as it was with both exogenic (chemotherapy) and endogenic factors (anemia, biochemical tumor process activity markers, age over 60).

Russian oncologists have also commented on the age-associated specifics of chemotherapeutic treatment, which is one more reason to bring together the two disciplines – oncology and cardiology [17]. Obviously, older people’s somatic status often implies a combination of oncological and cardiovascular disease, which makes it necessary to combine the treatment by two experts, and sometimes even call in the gerontologist.

It would be probably fair to say that, in Russia, the first discussions on therapeutic treatment and rehabilitation of cancer pa-

tients, as well as the problems of cardioncology, took place at the conference *Multifield Clinic in Solving Problems of Oncological Patients*, which was held in St. Petersburg Clinical Hospital of the Russian Academy of Sciences (RAS) in December 2012. The honorary guest and lecturer at the conference was Dr. Carlo Ci-polla, Head of the Cardiology Department at the European Institute of Oncology, President of the International Cardioncology Society (Euroasia), who read a paper entitled *Cardioncology, the New Medical and Ethical Issue*. The conference took place against the background of intensive debates among Russian oncologists concerning the advisability of transferring all cancer treatment to specialised centers, which at present totally lack well-equipped therapeutic, to say nothing of cardiologic, departments and services. In this respect St. Petersburg Hospital of RAS has always had unique experience in multi-field treatment of oncological patients. This experience was later presented in a number of papers read at various conferences and published in journals [18].

True, during this last year the subject of cardiac toxicity has also become topical among cardiologists. Thus, at the Russian National Congress of Cardiologists in 2013, a clinical symposium was arranged entitled *Cardiology and Oncology: Time for Joint Action*, while the congress papers included a thesis on the possibility to diagnose and prevent anthracycline cardiac toxicity using ivabradine [19].

Thus, the need for interdisciplinary cooperation with oncologists is gradually being recognised by our cardiologists. The process has started and is going on. We think it should not be limited to the problems of cardiotoxicity, because it is not only the consequences of chemo- and radiotherapy that contribute to the problems of cancer patients. One more frequent pathological manifestation of tumors are systemic reactions of the organism, or the so-called paraneoplastic syndromes, which our studies are specifically focused on [18]. Besides, development of organisational and medical methods of therapeutic and cardiologic cancer patients’ rehabilitation also deserves special attention. Our views on these matters will hopefully soon be published in the paper entitled *Cardioncology in the Treatment Regimen of Cancer Patients* (Russian Journal of Cardiology).

At present, the advancing discipline, cardioncology, which is designed to develop new tasks of cardiologic curation and rehabilitation of cancer patients, is very topical, and its development requires the concentrated efforts of medics from all over the world, which is obviously also true for the medics of the Russian Federation.

*Prof. Marina Ballyuzek is the member of European Society of Cardiology, Heart Failure and the member of Russian Society of Cardiology*

## References

1. The situation of cancer care in Russia in 2012. Caprino AD, Starinskiy VV, Petrova GV (ed.). FSBI "P.A. Herzen MRIO", Russian Ministry of Health, 2013.
2. News bulletin No. 297 SMI WHO, February 2012.
3. GLOBOCAN, 2008 [online: <http://globocan.iarc.fr>] (access: 19.04.2011).
4. Shalnova SA, Conradi AO, Karpov YA et al. Analysis of mortality from cardiovascular disease in 12 regions of Russian Federation involved in the study Epidemiology of cardiovascular disease in different regions of Russia. *Russian Journal of Cardiology* 2012; 5(97).
5. Hershaw ML, Orlova RV, Moiseenko VM. Prevention of cardiotoxicity caused by doxorubicin (adriamycin) using Cardioxane (ICRF-187, dexrazoxane) in polychemotherapy of advanced breast cancer. *Oncology Issues* 1993; 39(1-3): 26-31.
6. Orlova RV. Evaluation of cardiotoxicity caused by antitumor anthracycline antibiotics and its possible prevention. Author's Ph.D. thesis. St. Petersburg 1995.
7. Timakov AM. Late cardiotoxic effects of chemoradiation therapy in children with hematological malignancies and other cancer diseases. Author's Ph.D. thesis. Moscow 1994.
8. Timakov AM. Long-term results of treatment of acute lymphocytic leukemia in children. Author's Ph.D. thesis. Moscow 2003.
9. Tarasevich RA. Anthracycline cardiotoxicity problem in anticancer therapy in childhood. *Questions of Hematology, Oncology and Immunopathology in Pediatrics* 2005; 4(1): 58-64.
10. Matyash M, Kravchuk TL, Vysotsky VV et al. Anthracycline-induced cardiotoxicity: mechanisms of development and clinical manifestations. *Siberian Journal of Oncology* 2008; 6: 66-75.
11. Matyash M, Kravchuk TL, Vysotsky VV et al. Cardiotoxicity of cytostatic drugs excluding anthracyclines. *Siberian Journal of Oncology* 2009; 5: 73-82.
12. Orel NF. Anthracycline cardiotoxicity: the possibility of overcoming. *Modern Oncology* 2004; 6(3): 121-124.
13. Semenova AE. Cardio- and neurotoxicity of anticancer drugs (pathogenesis, symptoms, prevention, treatment). *Practical Oncology* 2009; 10(3): 169.
14. Chernov VI, Kravchuk TL, Zelchan RV, Goldberg VE. ECG-gated single-photon emission computed tomography in the evaluation of cardiotoxicity of doxorubicin. *Nuclear Medicine and Radiation Safety* 2012; 4: 32-38.
15. Boqueria LA, Malashenko AI, Kavsadze VE, Serov RA. *Cardiooncology*. NCCS A.N. Bakuleva RAMS 2003: 254.
16. Dolgih TY, Jeltova LI, Domnikova NP et al. The state of autonomic nervous system of the heart in patients with non-Hodgkin's lymphoma during chemotherapy. *Fundamental Research* 2012; 5: 26-30.
17. Moiseenko VM, Prochenko SA. Chemotherapeutic aspects of the treatment of tumors in the elderly. *Biomedical Journal, Medline.ru*. 2002; 3: 267-268.
18. Ballyuzek M. F., Stepanov B. P. Aims and opportunities of therapeutic rehabilitation of oncology patients. *Clinical medicine/Klinicheskaja medicina* 2013; 9
19. Vasyuk Yu A, Shkolnik EL, Nesvetov VV et al. Opportunities of early diagnostic and prevention of anthracycline cardiotoxicity by inhibiting F-channels of sinus node with ivabradine. *Materials of Russian National Congress of Cardiology "Cardiology: from science to practice"*. St. Petersburg, 2013: 0129.

### Correspondence:

Prof. Marina F. Ballyuzek, MD PhD  
Department of Cardiology, St. Petersburg Hospital of Russian Academy of Sciences  
St. Petersburg, pr. Toreza 72, 194017, Russian Federation