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The Red Beam: Past, Present, and Future of Radiation Oncology in Russia

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History of Radiation Oncology in Russia

The history of medicine and science in Russia is full of global "firsts," and Russians are rightly proud of this scientific heritage. Even non-Russians with a working knowledge of scientific history can cite, for instance, that the periodic table of elements was conceived by Dmitri Mendeleev, the first virus was isolated by Dmitry Ivanovski, and the first extraterrestrial satellite placed in orbit and first manned space flight, respectively, were accomplished by teams of Soviet scientists and engineers. However, despite this auspicious history, scientific progress in Tsarist Russia and the Soviet Union was not immune to the historical convulsions of the 20th century. Consequently, rather than a steady march of progress, the history of Russian science can better be described as a cycle that alternated between periods of great discovery and intervals of repression and backsliding. The specific disciplines of radiation biology and nuclear medicine were not exempt from the ebb and flow of this historical pattern.

Within the Russian scientific tradition, radiation and its application in oncology have deep roots. Therapeutic radiation therapy in Russia dates back to 1903, when a radiation oncology department was formed in what is the oldest cancer center in Europe: the P. Hertzen Moscow Oncology Research Institute. That year, in an inspiring act of multinational collaboration, Marie and Pierre Curie personally gifted radium salts to the director of the Institute, Professor V. M. Zikov, and the founder of the radiation oncology department, Professor D. F. Reshetillo. It was Reshetillo who first explored the use of radium preparations to treat various malignancies and in 1906 published what might be the world's first clinical textbook of radiation oncology, *Treatment by Roentgen Rays with a Preliminary Account of Roentgenology and Roentgenodiagnosis*. In 1910, he published another seminal monograph, *Radium and Its Applications in Medicine*. Like his American contemporaries, Halsted and Osler, Reshetillo defined himself as a physician-scientist. He and his disciples spent their careers dissecting the fundamental questions in radiation oncology and were among the first in the world to publish on the effect of dose, fractionation, treatment time, and hypoxia on clinical outcomes. As a result of these pioneering efforts, both at bench and bedside, radiation therapy became a standard modality in the treatment of malignant tumors in Russia as early as the 1910s.

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This head start in radiation oncology as a distinct medical and scientific discipline was interrupted by the first of the 20th century's "times of troubles" in Russia. Within a 10-year interval spanning 1914 to 1924, Russia experienced a series of paroxysms, including World War I, the October Revolution, and the Russian Civil War. This period was characterized by economic depression and mass starvation. However, despite these grave conditions, a few brave Russian scientists persevered to continue the study of radiation and its use in medicine. In fact, 2 facilities devoted to radiation therapy were commissioned during this period. The State Institute of Roentgenology and Radiology was founded in 1918 in St. Petersburg (then Petrograd) and the Roentgen Institute was founded in 1924 in Moscow.

These centers were instrumental in educating several generations of radiation oncologists, physicists, and radiobiologists and are still open to this day. The P. Hertzen Moscow Oncology Research Institute was the stronghold of clinical radiation oncology. The Roentgen Institute focused on radiation physics and the development of radiation equipment. Finally, the State Institute of Roentgenology and Radiology was devoted to radiation biology.

The Russian radiation biology program, in particular, left a truly global mark. The work of 2 men, Nikolai Koltsov and Nikolai Timofeev-Ressovksy, illustrate this impact. Koltsov, a zoologist and early geneticist, laid much of the groundwork for molecular genetics in the early part of the 20th century. A brilliant theoretician, he postulated in 1927 that inherited traits were likely to be passed on by a "giant hereditary molecule" consisting of "two mirror strands that would replicate in a semiconservative fashion, using each strand as a template" (1). His hypothesis, of course, turned out to be an uncannily accurate prediction of DNA, made nearly 3 decades in advance of the diffraction experiments of Watson, Crick, and Franklin.

Koltsov's brightest pupil, Nikolay Timofeev-Ressovsky, became a pivotal figure in genetics in his own right (Fig. 1). His contribution was to bring together the work of biologists, chemists, and physicists to lay down the basic principles of molecular mutagenesis and radiation biology. His early work on these subjects culminated in a foundational text of 20th century genetics, which he wrote with co-authors Karl Zimmer and Max Delbruck: *On the Nature of Gene Mutation and Gene Structure* (2, 3). Among the radiation biology principles expounded in their publication was the concept that radiation mutagenesis involved a "hit" by an ion pair on a "target" molecule. Again, this theory was postulated well before the specific nature of ionizing radiation's interaction with DNA strands was described.

A tragic footnote to Timofeev-Ressovksy's scientific discoveries was that his academic career was spent in the shadows of both the German Third Reich and the Soviet Union. He and his family were not immune to the political movements and bore the brunt of multiple oppressions. In Nazi Germany, his first son was killed at the hands of the Gestapo, and after World War II, Timofeev-Ressovsky moved back to the USSR, where he was arrested and incarcerated in the notorious Gulag. However, in a testament to his spirit and love for science, after his liberation, he continued to work productively as a scientist, generating new discoveries well into his sixties.

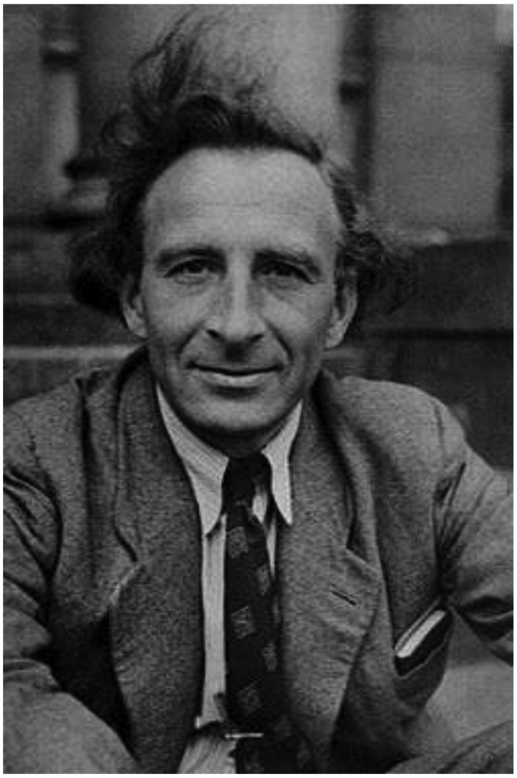

Fig. 1. Nikolay Timofeev-Ressovsky (photographed during his residence in Germany).

A silver lining to Timofeev-Ressovksy's international career was that, while in Germany, he influenced an entire generation of molecular biologists who went on to advance the fields of genetics and radiation biology in centers across North America and Europe. The pollination of his research outside the Soviet sphere turned out to be a fortuitous dodge as another destructive historical force came to the fore within the USSR. In the mid-20th century, legitimate biologic investigations in Russia were abruptly frozen by the advent of so-called Lysenkoism. Trofim Lysenko rose from modest beginnings in a peasant family to serve as the director of the Soviet Union's Academy of Agricultural Sciences. In this position, he made fantastic promises of agricultural productivity based on the Lamarckian principles of heritability. In essence, he argued that a single generation of a crop could be "taught" certain advantageous characteristics and that these characteristics would then be passed on to subsequent generations. This idea—which had already been refuted by Mendelian and Darwinian genetics—was naturally disputed by mainstream biologists. However, the marriage of Lysenkoism with the Soviet apparatus's revulsion to dissent resulted in the persecution and suppression of scores of Russian scientists, many of whom perished in concentration camps.

Although the effect of this human tragedy on Russian science cannot be underestimated, the second half of the 20th century again demonstrated the Phoenix-like ability of Russian science to recover and rise to new heights. As Lysenkoism buckled under the weight of its contradictions, the next generation of biologists regained their voice to make new fundamental discoveries in radiation biology. Among these were N. V. Luchnik and V. I. Korogodin, who in the 1960s and 1970s made essential discoveries in the study of genetic repair mechanisms after radiation injuries. For instance, Luchnik was the first in the world to show that ionizing radiation could result in chromosomal damage, and Korogodin made the discovery that homologous recombination was a mechanism for repair of such radiation insults. This scientific resurgence in radiation biology continued into the 1980s as the late Soviet Union regained a rigorous scientific footing. Book titles from this era demonstrate this re-emergence of sound genetic principles in the study of radiation biology:

- *Cellular Tumor Response to Radiation and Chemotherapeutic Damage* (I.I. Pelevina, G.G. Afanasiev, G. Gottlieb, 1978)
- *Radiobiology of Stem Cells* (A.G. Konoplyannikov, 1984)
- *Genetic Control of Radiosensitivity Modification* (V.G. Petin, 1987)
- *Predictors of Tumor Response to Radiation and Drug Therapy* (A.N. Dedenko, I.I. Pelevin, A.S. Saenko, 1988)

Many of the experiments from this era were performed at the Obninsk Power Plant near Moscow, the first grid-connected nuclear power plant in the world.

No parallel to Lysenkoism occurred in the fields of physics and engineering, and Soviet investment in these areas was second to none. As early as the 1940s, the Russian physicist Vladimir Veksler invented a microtron particle accelerator (4). During the interval from 1950 to 1990, Russian technology in radiation oncology progressed from the use of gamma rays with cobalt-60 sources—first adopted using a Soviet model GUT-Co-400—to the installation of betatrons in the 1960s and linear accelerators in the 1970s. A Soviet compact betatron BM-10 was the primary method of electron beam therapy (Fig. 2). Intraoperative electron therapy became popular in the 1980s for the treatment of a wide variety of malignancies.

Russian technologic prowess in radiation oncology in the 1980s came to parallel that of the United States and Western Europe, and toward the end of the century, the development of a compact linear accelerator with 18 MV capabilities was actively pursued in the USSR as a subject of applied research, nearly in lockstep with similar efforts in the West. Of course, the fall of the Soviet Union in the 1990s and the period of instability afterward curtailed progress, and this endeavor was ultimately abandoned.

One of the most robust contributions to radiation science in Russia has been the rich clinical experience with protons.

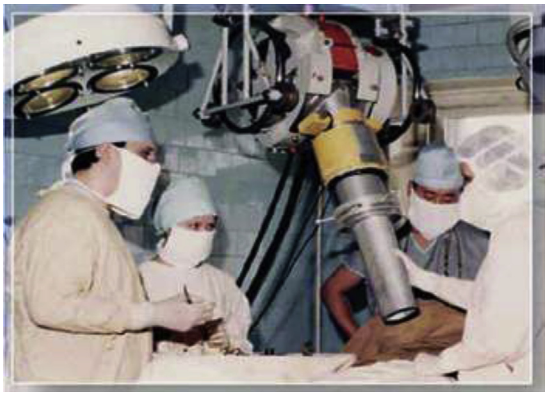

Fig. 2. Soviet betatron BM-10 used for intraoperative therapy (circa 1989s).

Currently, Russia has 5 proton centers, 3 of which have operated for decades. The aggregate clinical experience of these centers boasted more than 5000 patients by 1990. The 3 original proton accelerators are located in Moscow, St. Petersburg, and Dubna and historically operated as part of large research laboratories. In the past 5 years, anchoring proton centers within a comprehensive cancer center (such as is done in the United States, Western Europe, and Japan) has been a priority. To that end, the Joint Institute for Nuclear Research, in conjunction with Ion Beam Applications, developed and constructed the C235-V3 proton cyclotron at the Dimitrovgrad Hospital. A second new proton center is scheduled to open in St. Petersburg in collaboration with Varian. Finally, a compact proton synchrotron, marketed in the United States by ProTom International, was originally designed and developed at the Lebedev Physics Institute in Moscow under the direction of Russian scientist Vladimir Balakin. This same group is currently working on compact ion therapy designs.

In reviewing this history, it is evident that the contribution of Russia to the field of radiation oncology is characterized in equal measure by triumphs and setbacks. Fortunately, as Russians themselves look back on this history from the vantage point of the present, they tend not to view this back-and-forth through a lens of trepidation and frustration. Rather, they carry a uniquely Russian sense of optimism, borne from the simple observation that, despite the vicissitudes of history, Russian science and Russian scientists have always endured.

Cancer in Russia

During the past 15 years, life expectancy in Russia has slowly improved, with the current average 77.2 years for women and 65.6 years for men. However, the cancer mortality rates in Russia far exceed those in the United States and Europe. According to a study published in *Lancet Oncology*, cancer accounts for 15% of the mortality in Russia and is second only to cardiovascular disease among all causes of death (5). The annual cancer incidence is approximately 560,000, a 20% increase over the past 10 years.

The most common malignancy among men is lung cancer (17.8%), followed by prostate cancer (14.3%), colon cancer (11.3%), non-melanoma skin cancer (10%), and stomach cancer (8.2%). Among women, the most common malignancies are breast (21.2%), non-melanoma skin (14.6%), colon (11.6%), uterine (7.7%), stomach (8.2%), and cervical (5.2%) cancer. In 2015, a query of the national registry identified 3.2 million cancer patients receiving treatment, which accounts for 2.25% of the Russian population. Particularly troubling is that one-quarter of Russian cancer patients die within a year of their diagnosis, a statistic that lags behind most of the advanced world. The mortality-to-incidence ratio is 0.72 for Russian men compared with 0.36 for American men (5).

The reasons for this daunting cancer burden and relatively poorer outcomes compared with the West are numerous and complex. According to the World Bank, modern Russia is an emerging economy in the upper middle income group among nations. Nonetheless, the per capita healthcare spending is lower than that in countries at the same income level. Also, disparities exist in the access to health care between urban centers and rural regions that extend across the vast Eurasian landmass. The distribution of sophisticated equipment favors large cities, such as Moscow and St. Petersburg, where the cancer outcomes more closely resemble those of the rest of Europe and the United States.

With regard to cancer risk factors, alcohol and tobacco abuse remain a major problem in Russia, although public health efforts seeking to address these lifestyle choices have had some success in reversing these trends. Finally, primary prevention through screening tests such as mammography, colonoscopy, and Papanicolaou smear is also prone to geographic variation across the expanse of the country. If these challenges are addressed, we can reasonably expect that Russia's cancer epidemiology will more closely approximate the patterns in the West.

Radiation Oncology in Present-Day Russia

Survey of the current state

Radiation therapy centers are primarily state owned in Russia and are part of either cancer centers or academic research institutes. The Ministry of Healthcare (Minzdrav) is responsible for the purchase of all equipment for state-owned clinics. A number of private ventures have also appeared in the past 2 decades and operate on a fee-for-service model. According to a 2015 survey, 125 radiation oncology centers are currently in the Russian Federation, with a total of 308 teletherapy units and 126 brachytherapy units. Notably, linear accelerators constitute only 44% of the teletherapy units. A massive modernization initiative has been implemented over the past 5 years to update radiation therapy equipment and software throughout Russia. Already, more than 50 Varian medical linear accelerators have been installed in Russian cancer clinics, and current expansion plans foresee an additional 20 new systems installed per annum in the coming years.

Table 1 Comparison between Russian and European radiation oncology equipment and staffing in 2014

Variable	Russia	Europe	Russia-to-Europe ratio
Teletherapy units (1000 units/1 million population)	2.13	5.54	0.38
Clinical radiation oncologists (no./1 million population)	7.3	12.8	0.57
Radiation physicists (no./1 million population)	2.7	7.6	0.35
Radiation therapists (no./1 million population)	6.7	26.6	0.25
Radiation courses per 1 radiation therapist annually	156.4	76.8	2.03

Even with this pace of renovation, more than one-half of all linear accelerators are less than 5 years old, and more than one-half of the gamma therapy units are older than 10 years. With this inventory of outdated equipment, the average downtime of a teletherapy unit is 55 days annually, which, in turn, has a detrimental effect on both the quality of care and the volume of patients treated. This state of affairs is a part of the reason that only 30% of cancer patients in Russia receive radiation therapy compared with 70% in other developed countries. In addition to this shortage of equipment, the number of medical physicists, dosimetrists, and radiation therapists in Russia does not match the needs of this country of 144 million. The differences in staffing and equipment between Russia and Western Europe are summarized in Table 1 (6, 7). It is worth noting that clinical radiation oncologists have reacted to the inadequacies of personnel by shouldering professional responsibilities that would not typically fall under their domain in other developed countries, demonstrating both devotion to their patients and a famous Russian characteristic—resourcefulness.

Residency and training

Approximately 60 medical teaching institutions are in Russia, divided into undergraduate, postgraduate, and continuing medical education. Undergraduate medical education is a 6-year program after high school. Entrance is granted based on competitive entrance examinations and interviews. All graduates are required to complete either a 1-year general residency (internatura) or a 2- to 3-year specialty residency (ordinatura). Only after successfully completing the internatura or ordinatura can physicians practice independently.

Russian physicians can specialize in radiation oncology by way of 2 paths: either by completing a 2-year program in radiation oncology or by completing an additional subspecialization (a 576-hour requirement) after a 2-year program in medical oncology. A physician must also pass a qualifying examination to be board certified in the specialty, akin to the American and European systems. To maintain the certification, radiation oncologists are required to perform 144- to 288-hour refresher training at an academic center every 5 years.

Russia has recently instituted a reform in the continuing medical education system, which requires physicians to participate in a variety of educational activities, including workshops, conferences, and specialty symposia. These are typically organized by the national societies of radiation oncologists, medical oncologists, and radiation physicists. The success of this new system is yet to be determined, but it clearly represents a national acknowledgement that busy clinicians need to keep up with the pace of innovation in radiation oncology by way of continuous education. Finally, a number of Russian language academic journals are devoted to furthering the science of radiation oncology. These include *Questions in Oncology*, the *Hertzen Oncology Journal*, *Practical Radiology*, and *Radiobiology*. Physicians have free access to these journals.

The Future of Radiation Therapy in Russia

Despite the challenges we have described, the Russian Federation still boasts great natural resources, industrial potential, a robust educational system, and a deeply rooted culture of excellence in physics and engineering. A recent series of international collaborations have already suggested that Russian radiation science is becoming revitalized. As mentioned, Russians have partnered with Ion Beam Applications, Varian, and Protom International on large and complex projects involving proton therapy. More recently, the European Center for Nuclear Research chose in December 2015 to build a supercollider in Siberia (Novosibirsk). This unprecedented new collider was designed by a Russian team and will measure more than 100 km, more than 3 times longer than the Large Hadron Collider in Geneva.

Although Russia's legacy in radiation oncology peaked in the 1970s, these green shoots give credence to the notion that Russia has the potential to again be a leader in radiation biology, physics, and clinical innovation. We hope that sustained investment in the cancer care delivery system will attract a new generation of ambitious Russian scientists and physicians to the field of radiation oncology. If this initiative succeeds, we have little doubt that these individuals will continue their venerable forbearers' tradition of profoundly advancing the field.

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