

## RESEARCH ACTIVITY AT THE INSTITUTE OF ONCOLOGY IN LJUBLJANA

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**Abstract** – Presented is the research performed at the Institute of Oncology in Ljubljana, and the perspectives of its development. During the past years, this activity in the field of oncology has been logically joined within the frame of a research project by the Research Community of Slovenia. Individual studies and their applicability are presented, and the need for future development plans and education of new researchers pointed out.

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### Report

**Introduction** – Ever since the establishment of our Institute, scientific research has represented an essential part of its activities. The very nature of oncology, due to numerous unexplained and unsolved problems, calls for permanent research and scientific confirmation so in the experimental laboratory as well as in clinical practice.

It would be impossible to present all the research work that has been carried out during the past half-a-century long period at our Institute. The results are objectively presented in the extensive bibliography (1, 2) comprising approximately 2800 different publications issued in the period from 1938 to 1988.

The beginnings reach back to the year 1920, when the late Dr. Josip Cholewa, the first chief of the Institute, had established during his work as a surgeon in General Hospital Brežice, a laboratory of experimental oncology. As a logical result of his endeavours, in 1938 the present institute of oncology was established under the name of The Institute for Research and Treatment of Neoplasms of the Ban's Dominion, one of its units being also a laboratory for animal experiments.

In the post-war period the research activity underwent a rapid progress and growth despite severe financial, technical and personnel restrictions. Physicians and other scientific co-workers of the Institute have participated with their work on several national and international scientific meetings. They have won Boris Kidrič Fund Award six times, and also many other prizes for their achievements in scientific research. In the past 15-year period (1965–1989) 26 co-workers have obtained a Doctor's degree, and 17 a Master's degree.

**Research programs and projects** – In 1982, a long-term research program in the field of oncology was developed at our Institute, comprising also some studies performed in other medical and nonmedical institutions in Ljubljana and other parts of Slovenia. This initial coordination program served as the basis for our clearly defined program for the mid-term period 1985–1990, which has been accepted by the Research Community of Slovenia as well. Thus, there are two cancer related research programs in Slovenia, e.e. URP »Oncology«, and the project on Cancer Diagnosis and Treatment, and Prevention of Disease-and-Treatment-Related Compli

cations«. Both programs are coordinated by the Institute of Oncology in Ljubljana, which performs a major part of the research program.

Apart from the above mentioned two main programs, a number of shorter and less extensive studies are carried out every year by the help of the Institute's own research fund intended for these purposes.

**International Collaboration:** The Institute of Oncology takes part in several international studies. This collaboration comprises research in the field of epidemiology as well as new multidisciplinary clinical trials carried out by specialized societies and groups. The Institute is a member of the International Union Against Cancer (UICC), and the Organization of European Cancer Institutes (OECI); within the frame of the latter organization, there is a specialized group of pathologists which comprises our pathologists as well.

Our collaboration with IARC (International Agency for Research on Cancer) in Lyon refers to the following three studies:

- International incidence of childhood cancer
- Cancer incidence in five continents
- Studies of second cancers in relation to chemotherapy
- European childhood leukemia incidence study

We collaborate with NCI (National Cancer Institute, Bethesda, USA) in two studies, i.e.

- Second cancers in relation to radiation treatment for cervical cancer
- Record linkage study of patients exposed to diagnostic iodine

Within the frame of EORTC (European Organization for Research and Treatment of Cancer) collaboration, we participate in the following two studies:

- Treatment strategy in Hodgkin's disease
  - Hyperfractionation in head and neck tumors
- Our active collaboration in the SIOP (Society of Pediatric Oncology) refers the following fields:
- Wilm's tumor trial and study
  - Neuroblastoma clinical trial

Besides that, we have been regularly participating in all the studies carried out by SEOG (South-Eastern European Oncology Group), LBSC (Ludwig Breast Cancer Study) and IBCS (International Breast Cancer Study), and FIGO (International Union for Gynecologic Oncology). Within the frame of EC (European Community) we have been included in the COST project (Cooperation in the Field of Scientific and Technical Research) as a coordinator for Yugoslavia.

Active bilateral collaboration has been established also with the following institutions: M.D. Anderson Hospital and Tumor Institute (Houston), Erasmus University (Rotterdam), British Columbia Cancer Research Center (Vancouver), Münster University, University of Ulm, K. Marx University in Leipzig, CNR Institute of Clinical Physiology (Pisa), Centro di Riferimento Oncologico (Aviano-Pordenone), as well as within the frame of GOCCNE (Gruppo Oncologico Clinico Cooperativo del Nord-Est) and others.

Institute's workers are active members of several international societies.

The obtained results of continuous research work and active collaboration have qualified our Institute to be entrusted with the organization of numerous national and international professional meetings on different problems related to oncology and its future development. Following are some more relevant scientific meetings that have been organized during the past decade, and which are believed to have contributed toward successful distribution and spread of scientific findings and knowledge in oncology:

International meetings:

- 1981 Alpe-Adria-Oncologia (Malignant melanoma, Tumor markers, Cancer control)
- 1983 UICC Postgraduate Course on Clinical Cancer Chemotherapy
- 1985 UICC Postgraduate Course on Clinical Cancer Chemotherapy
- 1987 Tutorial on Monoclonal Antibodies in Hematopathology
- 1987 Eso Postgraduate Course on Principles and Practice in Radiotherapy
- 1988 International Slide Seminar on Cytomorphology of non-Hodgkin Lymphoma
- 1988 IIIrd International Meeting on Aids and Related Conditions, Breast Pathology and Technological Advances in Pathology
- 1989 IARC International Course on the Epidemiological Aspects of Occupational Cancer
- 1989 Alpe-Adria Meeting on New Achievements in Radiotherapy

#### **United Research Program (URP) Oncology:**

This program joins collaboration of several research institutions:

- The Institute of Oncology, Ljubljana
- Faculty of Medicine, University of Ljubljana, and the affiliated research institutes, Ljubljana
- J. Stefan Institute, Ljubljana
- Biotechnical Faculty, University of Ljubljana

The research projects are logically distributed into the following topic groups:

- carcinogenesis
- growth and characteristics of tumors
- host-tumor relationship
- detection and diagnosis of cancer
- cancer treatment
- prevention and sequelae

Within URP, the Institute of Oncology covers most of the mentioned topics. The following studies are carried out:

- Lobular carcinoma of the breast – a retrospective and prospective morphologic study (Lamovec J. et al.)
- Factors in the ascites of patients with malignant diseases affecting the transformability of normal cells in vitro (Škrk J. et al.)
- Computer analysis of cell images (Uskrašovec M. et al.)
- Pathogenesis of Hodgkin's disease (Zwitter M. et al.)
- Immunological characteristics of patients with malignant diseases (Krošl G. et al.)
- Intestinal damage after radiotherapy and chemotherapy (Lukič F. et al.)
- Soluble cell products and their biological significance (Serša G. et al.)
- Malignant lymphomas of non-Hodgkin type – a prospective study (Jančar J. et al.)
- Pathology of malignant soft tissue tumors (Golouh R. et al.)
- Solving the problem of small population based areas for the analysis of rare diseases (Pompe Kirn V. et al.)
- Doctrinary problems of the diagnostic algorithm of X-ray imaging methods in oncology (Us J. et al.)
- Problems of intensive treatment of cancer patients by autologous bone-marrow transplantation, chemotherapy and whole body irradiation (Rufolf Z. et al.)
- Comparison of metastasizing characteristics of malignant tumors (Plesničar S. et al.)
- IBCS VI + VII: Adjuvant chemotherapy in patients with operable breast cancer and confirmed lymph node involvement, and of highrisk patients without evidence of lymph node involvement (Lindtner J. et al.)
- Local application of human leukocyte interferon (HLI) in patients with malignant diseases (Jereb B. et al.)
- Microwave local hyperthermia in the treatment of advanced superficial malignant tumors (Budihna M. et al.)
- Problems related to the chemotherapy of head and neck tumors (Auersperg M. et al.)
- Optimum dose-time-volume relationship in

radiotherapy of gynecological cancer (Kuhelj J. et al.)

- Cryosurgery in oncology (Šušteršič M. et al.).

**Cancer Diagnosis and Treatment, and Prevention of Disease-and-Treatment-Related Complications:** This project is carried out by the following institutions:

- The Institute of Oncology, Ljubljana
- General Hospital Maribor
- Clinics of University Clinical Center in Ljubljana

A relevant part of the investigations is performed at the Institute of Oncology which functions as a coordinator. The research is primarily directed to clinical applicability and the transfer of basic knowledge into daily practice. The research project carried out at the Institute of Oncology comprises the following studies:

- Combined treatment of advanced esophageal cancer (Benulič T. et al.)
- Treatment of urological complications due to radical therapy of gynecological cancer (Fras P. et al.)
- Treatment of gastrointestinal tumors – adjuvant postoperative treatment of gastric and colorectal cancers (Markovič S. et al.)
- Pain control by intrathecal application of opiates and similar drugs combined with electrostimulation (Mavrič O. et al.)
- Psychoimmunologic factors in the etiology and prognosis of malignant testicular tumors (Pirc B. et al.)
- Late results of the treatment of gynecological cancer in relation to prognostic factors (Ravnihar B. et al.)
- Study of the treatment of testicular tumors – a model of team approach (Stanovnik M. et al.)

The impact of our research work is evident from the bibliography which is part of the annual reports (3, 4, 5, 6, 7). Here it should be mentioned that in the years 1984–1988 some of our investigators appeared as first authors in Science Citation Index altogether 317 times (8).

**The Research Fund of the Institute of Oncology:** The Institute's own research fund established in 1961 is intended mainly for short-term studies. Some of them have been completed already, whereas the others are still under way. Following are some of the studies in question:

- Regional cancer problems in Slovenia – incidence in relation to outside factors

– Registration and computed data processing of cancer patients treated by radiotherapy at the Institute of Oncology

– Treatment of colorectal cancer at the Institute of Oncology during the years 1971–1981 – a basis for prospective study

– Tumor markers in lymphomas – LDH with isoenzymes, microglobulins, ferritin

– Adjuvant chemo- and radiotherapy in patients with operable breast cancer in the years 1975–1980 at the Institute of Oncology

– New possibilities in the treatment of fungoid mycosis

– Influence of radiotherapy on the treatment of meningeoma

– Detection of medullary thyroid carcinoma (MCT) and accompanying multiple endocrinopathies (MEN) in close relatives of patients with confirmed MCT

– Value of cytochemical reactions in fine-needle aspiration biopsy samples of the lymph nodes in non-Hodgkin malignant lymphomas

– Brain metastases of unknown origin

– Tumor site as a prognostic factor in small-cell lung cancer

Our particular attention is paid to the renewal of our scientific research staff potential; thus, the majority of younger co-workers are encouraged to perform investigations for obtaining doctor's and master's degree. Within the frame of the action »2000 young investigators« five new research workers have been employed at our Institute.

In the past few years, some studies aimed at the introducing of new treatment methods, as well as long-term projects of general national interest have been financially supported by tender published every year by the Health Community of Slovenia. Following are some more relevant of these projects:

– Intrathecal application of chemotherapy using access-port valves

– New split-dose irradiation regimens

– The use of new tumor markers in the diagnosis of malignant diseases

– Registration and computed data processing of cancer patients treated at the Institute of Oncology in Ljubljana

– Development of standard dosimetry for the needs of radiotherapy

– Flow-cytometry in the diagnosis of malignant tumors and its use in following the effectiveness of chemotherapy

– Intraarterial chemotherapy of specific types of malignant tumors

Among the research projects dealing with the development of the strategy of cancer control, the following studies should be mentioned:

– Regional cancer problems in Slovenia

– Multivariate data analysis of cancer incidence in reference with outside factors

– Evaluation of breast cancer risk in reference with oral contraceptive use

– Education on cancer in Slovenian population

– Pilot study on breast cancer screening program for female population of Slovenia.

Apart from all the above mentioned activities, a successful collaboration has been established between the Institute and other institutions, so on regional as well as on federal basis, e.g. YUGOS (Yugoslav Group of Oncological Studies).

The Institute's INDOC center with specialized library comprising 8990 books and 173 current periodicals enables an accurate and on-line access to the data from scientific publications elsewhere, and thus promotes a more efficient international collaboration and research work.

**Conclusion** – Scientific research has always been and will remain one of the priorities of our Institute's further development. Looking back with pride at our achievements of the past 50 years, we do not have to fear for the future of our research work, despite the restricted facilities and limitations we have to face; promising young investigators hat have successfully started to replace their senior colleagues are a guarantee of the success. Steady increase in the number of scientific publications can be considered a reliable indicator of the quantitative as well as qualitative growth of our research work.

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