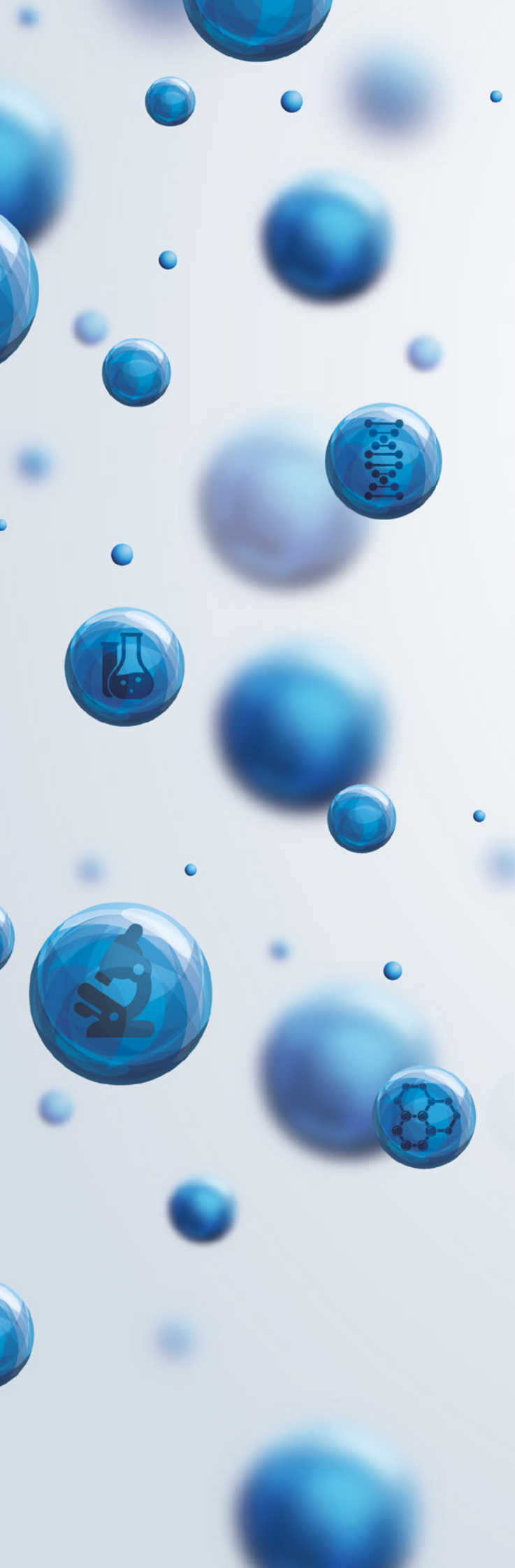


Fondazione IRCCS
Istituto Nazionale dei Tumori

Sistema Socio Sanitario

Regione Lombardia

SCIENTIFIC REPORT

2016-2017

CONTENTS

INTRODUCTION

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES 22

DEPARTMENTS AND UNITS 38

ADDITIONAL INFORMATION 102

* See Appendix for more information at http://bit.ly/2aYvFiB

FROM THE PRESIDENT

ENZO LUCCHINI

Since January 1, 2016 I have been the President of Fondazione IRCCS - Istituto Nazionale dei Tumori, the historical oncology center envisioned by Luigi Mangiagalli and inaugurated on April 12, 1928, by Vittorio Emanuele III. The Istituto Nazionale dei Tumori in Milan was the first center in Italy to organically address the "dark evil", a term used by Carlo Emilio Gadda to name cancer in his novel "The pain cognition" of 1941. Today the Institute has grown to the point that it has become a reference of great international prestige for the research and treatment of cancer, a "horizon of hope" for so many patients who come not only from all Italian regions, but also from abroad. The Institute I chair represents a human, cultural, scientific and technological heritage for both the Lombardy Region, for Italy, and also abroad. INT is an international cancer center certified by the Organization of European Cancer Institutes (OECI) as a "Comprehensive Cancer Center".

The Institute site is a composite hospital structure where research activity is closely connected to the clinical dimension of care. In Luigi Mangiagalli's time, the "dark evil" would lethally affect about 25 thousand people because of the lack of good treatment and care, including untold suffering. Today in Italy there are about 365 thousand new cases diagnosed each year. Thanks also to the contribution of our Institute, cancer deaths in recent decades have decreased by 18% among men and 10% among women. These results were achieved thanks to prevention and research activity and thanks to the new therapeutic options which have become available for the most common cancers as well as for the most rare, investigated here and treated with excellence.
Thus, the INT stands for its patients as a "horizon of hope": through its multifold excellence and a continuous collegial effort towards innovative frontiers of research, immediately translating the latest evidence in the fields of prevention, diagnosis and treatment into practice.
The underlying feature to this is INT's signature: attention and care to the person affected by the disease, not to the disease alone.

The present years are posing a striking paradigm shift, as evidenced by data from AIOM (Italian Oncology Association) and AIRTUM (Italian Association of Cancer Registries).
In comparison with the 365.800 cancer cases diagnosed in 2016, 369.000 new cancer cases were diagnosed in 2017 (i.e., 192.000 among men and 177.000 among women).
These numbers - over 1.000 diagnoses a day - are linked to several factors (better widespread health education and the availability of advanced diagnostic technology surely play a key role) and thanks to progresses in research and innovation they translate in a constant increase in the number of people surviving a cancer diagnosis.
According to available estimates, 3.304.658 cancer survivors could be counted in 2017, 5,4% of the entire population, marking a 24% increase compared to 2010. It is possible to assess that 27% of these are cured, whereas 20% live with cancer for an increased period of time.
These important numbers point a need for change not only from the clinical perspective, where already the chronic disease care model is being adopted in oncology, but also from the social perspective, in relation to everyday life, touching economical and occupational issues.
Despite the numerous steps taken in the field of occupational rights and cancer, about eight patients out of ten face life changing drifts regarding their jobs, from wage reduction to redundancy. It is often a struggle for cancer survivors to activate or keep health insurances or life policies, even though these are required as a guarantee for morgages and loans.

FROM
THE SCIENTIFIC DIRECTOR

GIOVANNI APOLONE

As part of the innovations introduced in the research policies over the last 2 years period, since I was appointed as Scientific Director of the Institute, I intended to propose a new and renewed publishing project for the Scientific Report. In my view, it should be issued on a two-year basis with an exhaustive presentation of projects, activities and results and comparative meaningful information on research results over a two-years period in order to provide an accurate framework of the trends and directions in research strategies.

As a transition to a new editorial project, the Scientific Report 2016 was published in 2017 in a summary form illustrating the main results achieved in 2016 and introducing innovative areas of research with a strong focus on the constant improvement of clinical outcomes.

I am now really pleased to present this new Scientific Report 2016-2017, that takes into consideration the assessment carried out by the Scientific Directorate at the end of the 2013-16 programming period of the 6 lines of research so far pursued.
The new Report, in addition to available research outputs, also considers the process that gave raise to new strategic directions towards 4 novel research lines - Primary prevention, secondary prevention and early diagnosis, Precision medicine and technological innovation (pharmacological and non), Complexity and rare tumors, Health care and "Outcome Research".
The new four research lines intend to offer a strong guidance and planning in line with INT mission and current priorities, as well as with the available resources.

It's worth remembering that the Foundation, thanks to the strong focus on translational research, where research activities and healthcare are connected through multidisciplinary programs designed and coordinated by science teams with diverse clinical and scientific backgrounds, was confirmed both in 2016 and 2017 as first among Italian IRCCS Cancer Institutes.

The scientific output in 2016 and 2017 has enjoyed an upward trend according to all standards conventionally used to classify research activity: the clinical trials conducted in 2016 were 644, and 633 in 2017. Over 25,000 patients per year had the opportunity to participate in research protocols that, besides offering them the best possible treatment, also gave them access to innovative drugs and devices. In 2016 we published 693 scientific papers (3.744 IF). A positive trend confirmed in 2017 regarding scientific publications: 702 with IF 4.808.

As anticipated, the years 2016 and 2017 represented a major turning point for research at INT. At the end of 2016, the

introduction of a new planning instrument was proposed, the Strategic Research Plan for the period 2016-2019 (INT SRP 2016-19), approved by the Scientific Institutional Committee and the Board of Directors.

The INT SRP 2016-19 is a four-year research plan agenda aiming at a better planning of the research strategy, a more consistent decision-making process for research projects and experimentations and a more intensive effort to rationalize research-supporting resources and structures.

In order to find the better mechanism for sustaining new important multidisciplinary projects and initiatives within the new strategic direction, the Scientific Directorate has introduced the necessary organizational changes and identified the funding mechanisms that should give INT freedom to use the resources from the different financing sources in a way that is consistent with the strategic choices INT made.

At this purpose, a research Fund dedicated to in-house research was created to support investigator-initiated projects, not necessarily related with drug research and development.

This Fund would enable to plan yearly interventions to promote in-house research and to meet better the needs of our Institute. In accordance to this, in 2016 and 2017 the Scientific Directorate invested part of the available resources of the Fund at supporting in-house research through the launching of competitive yearly peer reviewed call with the aim to support preclinical and clinical multidisciplinary projects and researchers in early stages of their career.

As a result, the Scientific Directorate has financed six multidisciplinary projects in 2016, among which two coordinated by Principal Investigators under 40, and in 2017 the total of 14 projects received a financing through the competitive procedure of the internal Call.

In accordance with the INT SRP 2016-19 and in line with the aim of strengthening INT's presence at international level, INT participates to several European networks.
In particular, I wish to remember that in 2016 INT started the process of joining Cancer Core Europe, a consortium of seven leading European Comprehensive Cancer Centers to promote joint translational and clinical research projects, where INT became a formal member since the end of 2017.

These outstanding results have been possible thanks to the committment of the General Directorate and the strong effort of all researchers, clinicians and the INT personnel.

FOCUS ON MAJOR EVENTS

2016

CALL FOR RESEARCH VALUE 2016-2017

In 2016 and 2017 INT promoted the Call for Research Value which aims to offer professional growth to INT researchers through the funding of multidisciplinary and innovative projects. The total allocated funds in 2016 were 3.000.000 € and 2.000.000 € in 2017.
6 projects have been financed by the Call in 2016 and 14 projects in 2017, belonging to the following categories:

- Multidisciplinary research projects
- Incoming Mobility/Reintegration Grants for young researchers
- Start-up support, proof-of-concept

JARC (JOINT ACTION RARE CANCERS):

Since 2016 INT coordinates the JOINT ACTION ON RARE CANCERS (JARC), a project funded by the European Commission Public Health Directorate involving 34 partners from 18 European Member States. The mission is to prioritise rare cancer, in the agenda of the EU and Member States, with a view to national cancer plans and quality of healthcare, harmonization of clinical practice, innovation through promotion of clinical and translational research. Moreover JARC aims to develop innovative and shared solutions, in the areas of quality of care, research, education and state of the art definition on prevention, diagnosis and treatment of rare cancers.

2017

INSTITUTIONAL RETREAT

INT's Scientific Director organized a 2-day meeting to discuss the future research strategies (Oreno di Vimercate, 17th-18th March, 2017, "La Ricerca che verrà"). The main aim was to foster a multidisciplinary discussion between healthcare professionals (including INT's representatives, key scientists from all over Italy and scientific journalists) on the relevance of IRCCSs in the framework of national healthcare and to identify research priorities and major lines of research.

VALIDATION PROCESS FOR IRCCS ROLE

The Italian IRCCSs are care centres of excellence pursuing research purposes mainly of clinical and translational character in the fields of biomedicine and public health, while delivering high quality healthcare services (art. 1 Legislative Decree No 288/2003).
Out of 1000 active hospitals in Italy, 49 are recognized as "IRCCSs" (Institutes for Research and Care), of these, 21 are public and 28 are private, unevenly spread out across the national territory.
With the Act of the Ministry of Health (dated 11/23/2017) the role of INT as an Italian IRCCS was reconfirmed.

CANCER CORE EUROPE:

From October 2017 INT is part of Cancer Core Europe (CCE), a consortium of 7 CCCs of excellence – Cambridge Cancer Center (Great Britain), Gustave Roussy Cancer Campus (France), Karolinska Institutet (Sweden), Netherlands Cancer Institute (Holland), Vall d'Hebron Institute of Oncology (Spain) and German Cancer Research Center/National Center for Tumor Diseases (Germany) – piloting a future multi-site, virtually connected "European Cancer Institute" for translational cancer research, covering proof-of-concept studies, innovative treatments, and outcomes research.
Cancer Core Europe's efforts look to pave the way for a multi-site cancer institute that will drive the development of new treatments and earlier diagnoses for patients and more effective cancer prevention for Europe's citizens.
In December 2017 INT was invited to participate to the Call 13 of IMI 2 (Innovative Medicine Initiatives) which deadline was February 2018.

2018 2019

STRATEGIC RESEARCH PLAN 2016-2019

In accordance with decree no. 76F/2016 of 28 October 2016 the Scientific Directorate promoted the Strategic Research Plan 2016-2019 (INT SRP 2016-19) which identifies the priorities that are going to impact on the upcoming development of research at INT and the corresponding lines of research.
Furthermore the SRP establishes the strategic research priorities and objectives for a four years period (2016-2019).
The INT SRP 2016-19 is the Scientific Directorate's policy document and has two main topics: to improve the planning of the research strategy and to have a more consistent decision-making process concerning research projects and experimentations; it is an intensive effort to rationalize research-supporting resources and structures.

THE ESSENTIAL ABOUT INT

SCIENTIFIC ACTIVITY

2016		2017
693	Publications	702
3,744.29	Impact factor	4,808.02
46.9 %	Publications as first/last author	45.9%

RESEARCH

2016		2017
644	Clinical studies (Total)	656
249	Observational studies	235
395	Experimental studies	421
24,443	Patients included in clinical studies (Total)	20,750
21,982	Patients enrolled in observational studies	15,829
2,461	Patients enrolled in experimental studies	4,921

RESEARCH FUNDING

2016		2017
26,523,468 €	Total	€ 27,800,757
7,302,433 €	Ministry of health	€ 7,000,971
12,765,866 €	Funding agencies	€ 12,305,054
3,530,260 €	Clinical trials	€ 5,486,946
2,924,909 €	5xMille*	€ 3,007,786

*Funds obtained by Italian Ministry of Health and Italian Ministry of Education (MIUR) through the allocation of 0.5 percent contribution of taxpayers income tax devolved to research institution of choice

CLINICAL DATA

2016		2017
482	Beds	482
18,294	Total inpatients	18,056
4,348	Of which day hospital	4,267
1,147,333	Consultations	1,214,986

PATENT PORTFOLIO

2016 - 2017

16	Total Patents
7	INT Owner
9	INT Co-owner

EDUCATION

2016		2017
179	Events/training courses	172
4,151	Participants	5,839
34,406	Formative hours	44,656

FACTS & FIGURES

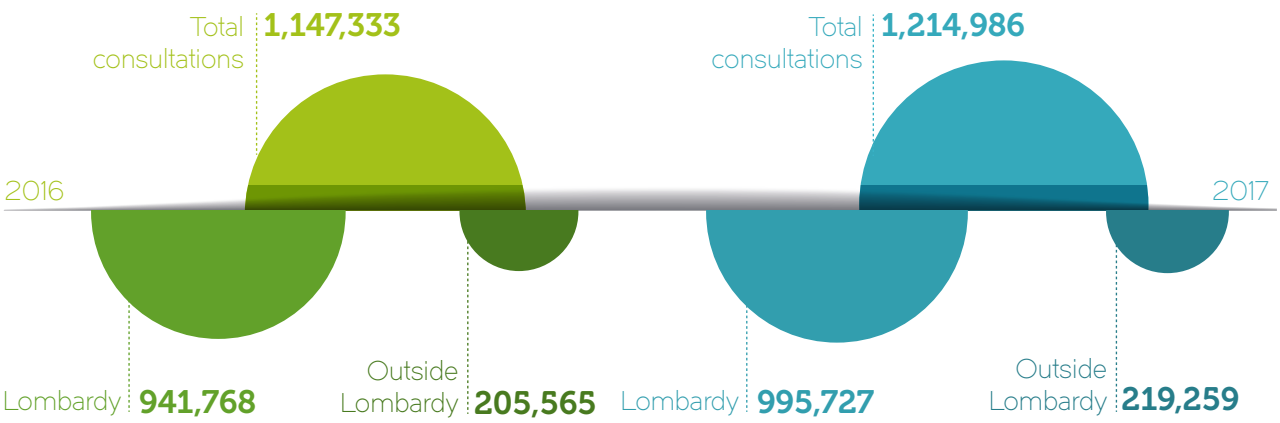
ACCREDITED BEDS 2016-2017

*Complex day hospital activity

HOSPITAL ADMISSION

	Total inpatients	
	2016	**2017**
Inpatients admission	13,946	13,789
Lombardy	8,927	8,846
Outside Lombardy	5,019	4,943
Day Hospital	4,348	4,267
Lombardy	3,319	3,318
Outside Lombardy	1,029	949

OUTPATIENTS VISITS



IMPACT FACTOR AND PUBLISHED PAPERS

CLINICAL STUDIES

RESEARCH FUNDING

	Total	Ministry Of Health	Funding Agencies	Clinical Trials	5x1000*
2017	27,800,757.53	7.000.970,98	12.305.053,98	5.486.946,04	3,007,786,53
2016	26,523,469.24	7.302.433,76	12.765.866,29	3.530.260,11	2,924,909.08
2015	26,609,858.60	7.546.313,34	13.443.081,54	3.354.000,00	2,266,463.72
2014	25,627,101.61	7.638.385,53	11.526.824,80	4.149.409,14	2,312,482.14
2013	26,900,636.40	8.052.592,96	13.548.844,54	3.039.755,47	2,259,443.43

*Funds obtained by Italian Ministry of Health and Italian Ministry of Education (MIUR) through the allocation of 0.5 percent contribution of taxpayers income tax devolved to research institution of choice

INSTITUTIONAL MAIN LINES OF RESEARCH 2013-2017

PREVENTIVE AND PREDICTIVE MEDICINE

Description

Research activity focuses on epidemiology and prevention through prospective epidemiological studies, case-control studies and survival studies. Our Institute coordinates National and International multicenter studies including European projects on rare tumors as well as interventional prevention projects. Our research on families with high genetic risk included a series of interventions developed towards people with a genetic predisposition to cancer and is carried out with the clinical and molecular haracterization of the involved genes.

Aims

Organization and implementation of interventional prevention projects, and management of the related biobanks. Creation of information networks based on data of population-based cancer registries. Determining the causes of survival differences present between populations of the same or of different countries; production of health indicators; promotion of information on health and healthy lifestyles; knowledge distribution of cancer epidemiology.

With regard to the familial-hereditary cancer: identification of individuals with increased genetic risk and of predisposing gene(s); coordination of correct surveillance programs and feasible options
for prevention; planning an adequate treatment in case of disease development.

STUDY OF THE MOLECULAR BASIS OF CANCER DEVELOPMENT AND PROGRESSION AND THE ROLE OF TUMOR-HOST INTERACTIONS

Description

Study of the molecular mechanisms (and their alterations) responsible for the origin, growth and progression of solid tumors and development of treatment approaches selectively targeting these mechanisms; Identification of tumor mechanisms of interaction with the surrounding microenvironment (stroma, immune system cells, extracellular matrix) during cancer progression, in order to elucidate biological events (such as tolerance of and resistance against tumor development) and investigate the link between inflammation and cancer; Definition of new therapeutic targets, diagnostic and prognostic biomarkers, as
well as predictive markers of response to conventional treatments.

Aims

Identification of molecular defects associated with cell transformation and tumor progression, to be used as markers for diagnosis, prognosis and disease monitoring. Detection and assessment of molecular targets against which to develop innovative treatments and clinical tests. Development of new drug combinations for advanced experimental systems.

INNOVATIVE PROBLEMORIENTED APPROACHES TO DIAGNOSIS AND TREATMENT

Description

Study of tumor-microenvironment interaction and identification of the molecular and genetic characteristics that can be translated into biomarkers for cancer diagnosis at its earliest stages.
Studies relative to the development of:

- radiopharmaceuticals for tumor characterization in molecular imaging and treatment;
- new drugs and/or treatment approaches for solid tumors, including clinical-translational studies prompted by the need for a) prognostic characterization of rare tumors ("big killers" that constitute yet an unsolved problem both from a diagnostic and therapeutic point of view);
  b) knowledge of the mechanisms responsible for the different degrees of radiotherapy toxicity in different tumor types;
- anticancer vaccines, genetic and biological therapies in certain tumors for the clinical testing of new substances.

Aims

Selection of biomarkers for early diagnosis, cancer risk assessment and treatment response; development of radiopharmaceuticals for biological characterization and use in imaging and treatment.

MULTIDISCIPLINARY DISEASE-ORIENTED APPROACH

Description

Interdisciplinary studies by organ disease including lung carcinoma, hepatocellular carcinoma, soft tissue sarcomas, tumors of the adult lymphohematopoietic system, and eventually other tumor types.
Enhance/intensify the relationship between preclinical and clinical research starting with novel molecular characterization techniques intended for new treatment approaches and a wider use of targeted molecular therapies.
Translational project development in the context of every single disease with operational support for the design and conduct of non-profit institutional clinical studies.

Aims

Promoting the development of a multidisciplinary disease-oriented approach across different types of cancer. Focal areas of study will be chemoprevention and treatment of preinvasive disease; early diagnosis; molecular typing and staging; conservative and minimally invasive treatment; targeted, biologically based therapies. Additional areas will include assessing the potential of individual patient tailored therapies (personalized medicine) using both conventional cytotoxic drugs and new molecular compounds to minimize toxicity.

INSTITUTIONAL MAIN LINES OF RESEARCH 2013-2017

APPROVED BY THE ITALIAN MINISTRY OF HEALTH

PEDIATRIC CANCER

Description

Studies of childhood tumors aimed at improving prognosis and reducing adverse treatment effects; studies focused on the prevention, early diagnosis and management of long-term cancer- and treatment-induced effects; when cure is no longer possible, focus on patient and family support to ensure they are not abandoned but fully supported (control of physical and psychological symptoms) and accompanied along the terminal phase of the disease.

Aims

Integrating longer survival and improving quality of life. For the most important childhood tumors (neuroblastoma, Wilms' tumor, Ewing's sarcoma), studies will seek to identify new therapeutic targets, thus new approaches to biological drugs, as well as assessing iatrogenic sequelae with respect to thyroid, cardiac, pulmonary and gonadal function in long-term cancer survivors.

PATHWAYS OF RESEARCH/ INTERVENTION AND ASSESSMENT OF QUALITY OF LIFE IN PATIENTS WITH CANCER

Description

Therapeutic and scientific activities have traditionally characterized medical oncology, but concrete operational and human support for cancer patients is equally important at a time when the humanization of cancer treatment is among the main goals of our Institute (as exemplified by the new hospice facility). Innovation in studies related to palliative care and rehabilitation is therefore fundamental. Palliative care has received increasing emphasis in recent years as a means to improve treatment and quality of life of cancer patients. With regard to oncological rehabilitation, information on the specific patient needs with debilitating treatment sequelae is still incomplete.

Aims

Assessment of analgesic therapy delivery, symptom control and supportive care (infusion of blood products, parenteral nutrition, etc.), comprehensive symptom and quality of life assessment, detection of markers potentially associated with the response to compassionate clinical treatment.

AWARDS AND RECOGNITIONS

ROBERTO BOFFI

Ambrogino d'oro awarded in year 2016.

UGO PASTORINO

Joseph Cullen Award for Research on Lung Cancer Prevention, from the International Association for the Study of Lung Cancer (IASLC-2016).

DARIO CALLEGARO

"Marzia Galli Kienle" SOS (Solidarietà in Oncologia San Marco) award 2016.

CHIARA TENCONI

Outstanding study Award at the World Congress of Brachytherapy 2016, San Francisco, USA. In Vivo Rectal Wall Dosimetry in Gynecological HDR Brachytherapy Using a Semi-Flexible Rectal Probe Provided with MOSkin Dosimeters".

LORENZO CASTAGNOLI

"Marzia Galli Kienle" SOS (Solidarietà in Oncologia San Marco) award 2016.

TIZIANA TRIULZI

Nastro Rosa Researcher 2016 award from LILT.

ANNAMARIA CERROTTA

Capri S.Michele Award - XXXIII ed.: Laura Rolandi 2016 Award.

AMELIA BARCELLINI

Eleonora Cantamessa Award 2017 IV ed.

PAOLO CORRADINI

Aura-Giffoni 2016 – SPECIAL AWARD FOR QUALITY OF WORK, DEVOTION AND GOALS ACHIEVED

CRISTINA BORZI

"Marzia Galli Kienle Prize" 2017 (Special Mention).

ALESSANDRA CATALDO

Special mention of Marzia Galli Kienle award for a published paper.

ALBERTO MUSSETTI

SOS (Solidarietà in Oncologia San Marco) award 2016
IV Ercole Brusamolino Award for young hematologists involved in lymphoma clinical or biological research, 2017.

CLAUDIA CAVATORTA

Best Poster Award at the PROS 2017 congress in New York, USA. Retrospective study of late radiation damages after focal radiotherapy for childhood malignant brain tumors.

FILIPPO PIETRANTONIO

Galli-Kienle award for research article on Cancer Discovery MET-driven resistance to dual EGFR and BRAF blockade (2017).

MARIO PAOLO COLOMBO

Prodi Lecture Award 2017.

MONICA TERENZIANI AND FILIPPO SPREAFICO

At SIOP meeting 2017 best poster awards and best clinical research to M.Terenziani and F.Spreafico.

MARTINA DI MODICA

Award for the best poster "4th PhD Students Meeting", Milan, 29-30 June 2017;
Award for the best poster "XVI NIBIT Meeting", Siena, 11-13 October 2017.

CLAUDIO VERNIERI

Conquer Cancer Foundation Merit Award of ASCO GU 2018 for the Abstract entitled "Prognostic and predictive role of Fumarate Hydratase in metastatic clear cell Renal Cell Carcinoma" (2017).

MARTA GIUSSANI

Piero Trivella Award for the best poster, "2nd Special Conference EACR-AACR-SIC", Florence, 24-27 June 2017.

AWARDS AND RECOGNITIONS

"SUBLINGUAL FENTANYL VERSUS SUBCUTANEOUS MORPHINE: A DOUBLE-BLIND PLACEBO-CONTROLLED RANDOMIZED CONTROLLED TRIAL"

Highest ranked abstract at the 9th World Research Congress of the European Association for Palliative Care, Dublin (Ireland), 9-11 June 2016.
Palliative care, Pain therapy and Rehabilitation Unit

"INTEGRATION OF PALLIATIVE AND ONCOLOGY CARE IN PATIENTS WITH LUNG AND OTHER THORACIC CANCER: REFERRAL CRITERIA AND CLINICAL CARE PATHWAYS"

Best young researcher poster "Berlucchi prize" at the Conference of the Italian Medical Oncology Association, Rome, 27-28 October 2017.
Palliative care, Pain therapy and Rehabilitation Unit

CEDRO D'ORO AWARD TO THE PARTECIPANTS IN THE YOUTH PROJECT IN 2017

Pediatrics Unit

"PREMIO INNOVAZIONE DIGITALE IN SANITÀ" AWARD

Impact category, promoted by Osservatorio Innovazione Digitale in Sanità, School of Management Politecnico of Milan (19/04/2017).
Immunohematology and Transfusion Medicine Service Unit

2017 ITWIIN (THE ITALIAN ASSOCIATION OF WOMEN INVENTORS AND INNOVATORS)

award for the patenting of 4-oxo-n-(4-hydroxyphenyl)retinamide derivatives, novel soluble compounds developed in our laboratories, as a therapeutic agents for cancer treatment.
Biomarkers Unit

BEST WORK OF THE YEAR ON THE BREAST JOURNAL 2016

Maria Carmen De Santis

The study "Factors influencing acute and late toxicity in the era of adjuvant hypofractionated breast radiotherapy"

LEADING CENTER IN LOMBARDIA FOR ONCOLOGIC LIVER TRANSPLANTATION

Gastrointestinal and Hepatopancreatobiliary surgery. Liver transplantation.

AWARDS AT INTERNATIONAL CONGRESSES

"Potential Clinical Impact Of The Introduction Of The Nonavalent Human Papillomavirus Vaccination: An Analysis Of 13,665 Patients Over A 18-Year Study Period". Esgo 2017.

"Assessing the Risk Occult Cancers and 30-day Morbidity in BRCAness Women Undergoing Risk-Reducing Surgery: A predictive Model and Nomogram". AAGL. Washington November 2017.

"Fertility-Sparing Surgery in High Risk Ovarian Cancer: Time for Overcome Initial Concerns" ISGE/AIGE congress Florence March 2016.

Gynecology Oncology Unit - Surgery

THE "PREMIO GIOVANI RICERCATORI" AWARD PROMOTED BY THE FONDAZIONE IRCCS INT

rewards young researchers that have distinguished themselves for their research output and results in clinical, basic and translational research.

The award was conferred to:

2016

Dario Callegaro
for clinical research

Lorenzo Castagnoli
for translational research

Elena Jachetti
for basic research

Michele Droz Dit Busset
award 2016 Maria Bambina Besana

2017

Maria Carmen De Santis
for clinical research

Martina Di Modica
for translational research

Maria Teresa Majorini
for basic research

Monica Niger
award 2017 Maria Bambina Besana

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

SCIENTIFIC REPORT 2016-2017

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

EARLY PHASE CLINICAL TRIALS

IMMUNOTHERAPY

EXPERIMENTAL ONCOLOGY AND MOLECULAR MEDICINE

OUTCOMES RESEARCH

PEDIATRIC ONCOLOGY

PREVENTION RESEARCH

RARE TUMORS

INNOVATION AND TECHNOLOGY: FOCUS ON SURGERY

EARLY PHASE CLINICAL TRIALS

OBJECTIVES

In line with its mission, INT has always promoted clinical research, both sponsored and investigator-driven. The high rate of clinical studies has been clearly facilitated by the activity of the institutional Clinical Trials Center (CTC), created in 2011 as a project of the Scientific Directorate which aimed at supporting investigator-driven, early-phase clinical trials and at helping researchers to manage spontaneous projects. Mechanisms' description of tumor transformation deriving from basic and translational research, leads to the formulation of innovative therapies, whose real efficacy will have to be demonstrated through clinical trials.
INT patients receive a variety of opportunities accessing sponsored and investigator-driven clinical trials, including early phase studies. This allowing the access to the most innovative treatments available. Most of the ongoing or planned early studies originate from the Medical Oncology and Hematology Department.

INT PATIENTS RECEIVE A VARIETY OF OPPORTUNITIES ACCESSING SPONSORED AND INVESTIGATOR-DRIVEN CLINICAL TRIALS, INCLUDING EARLY PHASE STUDIES

ACTIVITIES

Among the clinical studies performed in INT, a total of 61 early phase trials (phase I, I/II and I/III), with at least one patient enrolled or in follow-up, have been completed in 2016-17, 28 of which started in the biennium.
Solid tumors represent the major disease category, with 17 active studies; patients carrying hematological malignancies, lung, head and neck, urinary tract, colorectal, epato-gastro-pancreatic cancer and melanoma were offered to be enrolled in 34 early phase trials, if eligible for study criteria.
In the pediatric field, INT has been identified as a National reference Center for academic and sponsored phase Pediatric I-II studies. In the last two years, patients have been enrolled or in follow up in 10 early phase (I and I/II) trials.

Mirroring INT impact as referral center, a big fraction of early phase clinical trials are sponsored by external entity. Nevertheless, it is worth mentioning that 20% of trials are investigator-driven, arising from the need to answer unmet clinical needs, and INT investigators are more than competent in the field to answer these needs.

OUTPUT

In 2016-17 INT has been AIFA certified for the conduction of phase I clinical trials, both profit and no-profit. Together with the establishment of a multidisciplinary program INT has began a referral center for phase I studies.

KEYWORDS

Early phase trials
Innovative therapies
Clinical trials center

IMMUNOTHERAPY

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

OBJECTIVES

Unleashing of the immune system with immune checkpoint inhibitors (ICIs) is one of the most promising strategies for cancer treatment.

The introduction in the clinical setting of antagonistic antibodies targeting CTLA-4 and the PD-1/PD-L1 axis has markedly reshuffled the available therapeutic options for different tumor types.
INT is at the forefront of clinical and pre-clinical research in the field of immunotherapy.
The major efforts at INT are dedicated to improve the clinical efficacy of cancer immunotherapy by exploring combination regimens; that may maximize the chances of response: to design new immunotherapeutic strategies based on combination/ sequences; of treatment working on different cancer types; and to apply immunotherapy even in the adjuvant and neo-adjuvant settings.
Moreover, in spite of remarkable results achieved over the past 8 years in treatment of tumors as melanoma and non small cell lung cancer (NSCLC), still a high fraction of patients does not achieve a clinical benefit from immune checkpoint blockade.
Therefore, INT is actively pursuing the identification of biomarkers of response or of resistance and deciphering of mechanisms of primary and acquired resistance to immunotherapy.
All these studies are ultimately aimed at providing relevant informations needed to achieve patient-tailored clinical management.

INT IS AT THE FOREFRONT OF CLINICAL AND PRE-CLINICAL RESEARCH IN THE FIELD OF IMMUNOTHERAPY

ACTIVITIES

Clinical trials.

Over the past years, INT has carried out and contributed to a large number of phase I to III clinical trials based on treatment of patients affected by advanced solid tumors with ICIs antagonistic antibodies targeting CTLA-4, PD-1 and its ligand PD-L1, in melanoma, NSCLC, renal, bladder, gastric and colorectal cancer. Furthermore several early phase trials are ongoing aiming at: i) testing combinations of different ICIs targeting emerging inhibitory receptors expressed by T lymphocytes, or immunosuppressive factors (such as IDO1) produced in the tumor microenvironment; ii) assessing the clinical efficacy of ICIs in the adjuvant and neo-adjuvant settings, iii) assessing the potential synergistic effects due to the combination of ICIs with chemotherapy or with target therapy. Most of these innovative trials are coupled to translational studies aimed at defining predictive biomarkers of response, as well as at understanding the main mechanisms of resistance.

Translational studies in immunotherapy.

Many efforts at INT were devoted to understand which immunological or molecular features are associated with response to immunotherapy. This goal has been pursued in different tumor types by associating treatment to a comprehensive characterization of biological samples from the patients. To this end the molecular characterization of the neoplastic tissues, to understand the genomic landscape and mutational burden of the tumors, has been associated with an extensive characterization of the immune contexture of lesions by immunoistochemistry as well as with the analysis of gene expression in the biological samples. Further efforts have focused on exploiting peripheral blood samples as an unique window on the effects of immunotherapy on the immune profile of circulating immune cells.

Pre-clinical experimental models.

INT has been focusing on exploitation of appropriate in vivo models to identify new molecular targets and/or to provide means to understand mechanisms of resistance to immunotherapy.
This also includes fostering a better understanding of the role of pro-tumoral or immunosuppressive immune subsets in hampering the efficacy of immunotherapy.

IMMUNOTHERAPY IS GRADUALLY BECOMING PART OF THE STANDARD REGIMENS OF TREATMENT

OUTPUT

Over the past two years INT has significantly contributed to several Phase II and III clinical trials of immunotherapy in a variety of solid tumors, including NSCLC, melanoma, renal, bladder, gastric and colorectal cancer.
Thanks to the results of these trials, immunotherapy is gradually becoming part of the standard regimens of treatment in several of these tumor types. In melanoma, treatment with anti-PD-1 in the adjuvant setting in Stage IIIb to IV has provided evidence for longer recurrence-free survival compared to anti-CTLA-4. In urothelial cancer different immunotherapy trials involving INT have achieved evidence for improved overall survival compared to chemotherapy in the advanced stage, second line setting and for durable response rates in first line setting. In advanced renal cell carcinoma, combination of anti-PD-1 and anti-CTLA-4 have significantly improved overall survival and response rates compared to Sunitinib. In previously untreated, metastatic NSCLC patients the association of immunotherapy targeting PD-1 with chemotherapy improved significantly overall survival and progression-free survival compared to chemotherapy alone.

KEYWORDS

Immunotherapy
Immune checkpoint inhibitors
CTLA-4, PD-1/PD-L1
Immunity

EXPERIMENTAL ONCOLOGY AND MOLECULAR MEDICINE

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

OBJECTIVES

The multidisciplinary perspective needed to gain new knowledge in cancer complexity becomes a reality at the Department of Research and the Department of Applied Research and Technological Development. A variety of approaches are used thanks to the availability of multiple infrastructures and resources, dedicated science technology platforms, excellent expertise and established internal, national and international research networks and collaborations.

Many research projects are ongoing to clarify the molecular mechanisms of cancer growth and progression, the multiple steps of the metastatic cascade, and resistance to conventional and target-specific therapeutic agents, as well as to identify and validate novel targets and strategies for cancer treatment and to overcome resistance.

MANY RESEARCH PROJECTS ARE ONGOING TO CLARIFY THE MOLECULAR MECHANISMS OF CANCER GROWTH AND PROGRESSION

ACTIVITIES

Major attention has been devoted to microenvironment an inflammation, with a core project involving several research teams focused on the identification of new molecules detectable in blood circulation that may have diagnostic and prognostic value at cancer onset or recurrence. Increasing attention has been given to the stromal cell components of the tumor microenvironment as active players in tumor progression.

Stromal cell components co-evolve with tumors to form functional units, which support tumor growth. In this context, transforming tissues release the molecules that are necessary for cross-communication with the bone marrow, which provides the stromal cell components necessary to build the favorable tumor microenvironment. The molecules responsible for such cross-communications intercepted and identified in the blood may be exploited as potential biomarkers of tumor recurrence.

Circulating miRNAs, that in principle can be provided by stromal cells, are predictor of incipient lung cancer earlier than spiral CT, supporting the possible exploitation of miRNA as diagnostic biomarkers. Several studies investigating the functional role of specific miRNAs are ongoing in the field of prostate, breast, thyroid, lung cancer.

Studies regarding the role of exosomes-secreted miRNAs in metastatic spread are ongoing in lung and breast cancer. Increasing attention is now given to the extracellular matrix (ECM) as new determinant of tumor aggressiveness and response to therapy and through its unexpected capacity to regulate innate immune cells present in the tumor microenvironment.

These cells have been shown to support the growth of tumors, which have escaped from adaptive immune-surveillance.

Other projects are aimed to shed light on the complex interaction between multiple signaling pathways and cellular microenvironment in the induction of Epitelial Mesenchymal Transition (EMT), a phenomenon that permits invasion, metastasis and resistance to therapy.

OUTPUT

Next Generation Sequencing (NGS) and high-throughput microarray analyses allowed us to capture the biologic complexity of cancer and to identify and validate (in independent studies and/or public datasets) robust metagene-based predictors, able to define among others: 1) low and high risk of relapse after adjuvant/neoadjuvant therapy in breast cancer; 2) a genomic profile predictive of response to cetuximab in head and neck squamous cell cancers; 3) a miRNA signature (MiROvaR) that is a predictor of epithelial ovarian cancer progression independently of other relevant clinical covariates; 4) plasmatic circulating miRNAs that allow early identification of breast cancer patients responsive to trastuzumab; 5) mutational profile from targeted NGS predicting survival in Low Dose CT screening-detected lung cancers.
Besides, by whole-transcriptome analysis of human HER2 positive breast carcinoma and transgenic mouse models, we provided evidence that d16HER2 splice variant sustain cancer stem cell expansion in breast cancer.

Experimental efforts have been also directed to the optimization of imaging techniques with immuno-imaging.

In this regard, we have developed an antibody fragment (scFv) targeted against PSMA, an antigen commonly found and overexpressed in prostate cancer cells.
Once the antibody fragment has been labeled with ^{123}I, it can then be employed to identify cancer cells and find possible relapses.
The same fragment ^{124}I labeled has already been used to conduct preliminary experiments of Positron emission tomography (PET) imaging with very promising results.
A GMP process is going to be set up and a phase I clinical trial is foreseen.

KEYWORDS

miRNA
Microenvironment and Inflammation
Immuno imaging
Biomarkers

OUTCOMES RESEARCH

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

OBJECTIVES

Outcomes research relies on observational studies investigating the effect of specific therapeutic procedures on patients' health: response to treatments, overall and disease free survival, cancer prognosis and survivorship, long and short term side effects of anticancer treatments, quality of life etc.
In INT outcomes research is based on: INT clinical/experimental data and data from population based cancer registries.

ACTIVITIES

Outcomes research using INT clinical and experimental data

To facilitate outcomes research in accordance with the OECI Recommentations, in 2012, INT has established the "Clinical Cancer Registry programme".
The feasibility of systematic cancer registration at INT has been first demonstrated with the creation of the institutional Breast Cancer Clinical Registry (BC-CR), now being extended to other neoplasms such as lung and pancreas cancer. The BC-CR systematically collects clinical, pathological, metabolic and biomolecular data of all cases operated at the INT Breast Surgery Unit. The INT clinical cancer registries are based mostly on automated collection of clinical and anagraphic information from institutional databases, periodically delivered to the Health Impact Unit. The BC-CR is functionally connected with the INT blood bank and the INT blood exam database and for each patients it is therefore possible to directly consult the original reports, and to retrieve additional information of interest for specific studies.

Outcome research based on data from population based cancer registries.

INT designed EUROCARE, the largest international collaborative population-based study on survival and care of cancer patients in Europe. The EUROCARE data base includes survival data of over 13,800,000 patients diagnosed since 1978 in 117 European CRs, with vital status information available updated to 31 December 2008 or later. Beside general survival, selected EUROCARE cancer registries collect high-resolution clinical information for samples of incident cancer cases. The aim is to help interpreting differences in cancer outcomes and survival, using data on diagnostic exams, patients and tumor characteristics, treatment and follow-up that are more detailed than those usually available in the routine activity of population cancer registries.

OUTPUT

- INT Breast Cancer Clinical Registry
- EUROCARE High Resolution – (breast, colorectal, lung, NHL, melanoma)
- Lombardy Cancer Registry - Varese Province
- Lombardy registry of congenital malformations and adverse pregnancy events
- Registry of hereditary digestive system tumors

KEYWORDS

Breast Cancer Clinical Registry
Population based registry
EUROCARE

PEDIATRIC ONCOLOGY

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

OBJECTIVES

The Pediatric Oncology unit of INT conducts clinical and research projects on typical solid cancers of pediatric and adolescence age, and represents a referral center for all the Country.

ACTIVITIES

Most members belong to a vast network of scientific societies in an international background that is at the origin of the majority of academic trials here driven.

Many of those are here nationally and/or internationally coordinated. Over 75% patients are treated within clinical controlled trials also including phase I and II with new drugs.

Patient management is based on a true multidisciplinary approach that includes diagnosis (with specific dedicated histological and imaging expertise), treatment (including interdisciplinary activity with the pediatric surgical unit and the pediatric radiotherapy unit, a Bone Marrow Transplantation Jacie approved program and a team dedicated to phase I-II therapy in patients with relapsing/refractory solid tumors). Psychosocial support both for kids and parents is provided since diagnosis and during all treatment and follow-up, as well as long term survivors program (for the follow-up of iatrogenic sequelae and social re-entry). Counselling and genetic testing are ad hoc provided and will be implemented. Scholastic career is daily followed with dedicated teachers of public school of any grade from nursery to secondary school end with tailored programs both in and out of the hospital. During 2016 and 2017, over 250 new patients/year were diagnosed and treated.

OUTPUT

Dedicated age-specific facilities and projects for adolescents (the Youth Project) have been developed and represent a model to promote the normalcy of our patients.

Patients are followed also in sports activities in an true indoor gym and outdoor with dedicated sport rehabilitators.

A program for terminally-ill patients has been implemented with involvement of a private organization that is able to take care of the patients even from initial diagnosis if needed for heavy symptoms to be treated or for very severe disease prognosis.

A total of 3 phase I and II trials, 8 academic interventional trials and 4 observational trials have been opened to accrual in 2016-17.

In 2017 an ocular oncological unit was also implemented for retinoblastoma treatment, ocular pathway glioma evaluation and ophtalmologic event care. A mean of 45 peer-reviewed papers are yearly published

KEYWORDS

Childhood tumors
Adolescents
New drugs
Follow-up
Sequelae

PREVENTION RESEARCH

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

OBJECTIVES

INT has been promoting awareness that lifestyle and early diagnosis can contribute to reduce tumor incidence and improve disease management.

INT is involved in primary prevention by large prospective studies on the association between diet, hormones, nutrition, lifestyle, genetic factors, and cancer risk.
Primary prevention at INT also aims at identifying the pathogenic role of pollutants and erroneous lifestyles, and correct them by means of intervention studies, to reduce the onset risk .
Detection of cancer at an early stage offers the genuine potential to reduce mortality with new chances of cure. INT is involved in research programs aimed at enhancing secondary prevention employing strategies directed to discovery and validation of biomarkers.

Medical genetics consultation is also offered with the aim of identifying individuals with increased genetic risk, proposing surveillance programs and preventive intervention

INT HAS BEEN PROMOTING AWARENESS THAT LIFESTYLE AND EARLY DIAGNOSIS CAN CONTRIBUTE TO REDUCE TUMOR INCIDENCE AND IMPROVE DISEASE MANAGEMENT

ACTIVITIES

Several randomized controlled trials (RCT) aimed at diet and prevention are ongoing: COS, a RCT of diet and physical activity in BRCA mutation carriers; TEVERE, a blinded RCT of diet and metformin for primary prevention of breast cancer; MeMeMe, a RCT of diet and metformin for primary prevention of age-related chronic diseases; DIANA-5, a multicentric RCT of a diet based on Mediterranean and macrobiotic recipes and principles, and moderate physical activity, in reducing additional breast cancer events in women with early stage invasive breast cancer at high risk of recurrence because of metabolic or endocrine milieu.

Intervention on smoking cessation is ongoing as well as the identification of genetic polymorphisms related to the possible response to antitabagic treatments in smokers and data collection of smoking cessation of hospitalized patients.

The European project Tack-SHS Horizon 2020 is investigating the tackling secondhand tobacco smoke and e-cigarette emissions, providing scientific evidence on exposure assessment, burden of disease, development and evaluation of interventions.

The bioMILD study, is the first large study with international relevance that uses a molecular biomarker as first-line test, in combination with spiral CT, to identify the nature of lung nodules and the diagnostic pathway. A completed recruitment of 4119 strong smoking volunteers enrolled, 81% of which with a three-years follow up.
The recently started SMILE project represents a randomized pilot study to assess the feasibility and safety of a multiple intervention program, aiming at reduction of mortality in lifelong smokers.

Research programs aimed at enhancing secondary prevention strategies.

In a particular condition of risk or pathology in progress, secondary prevention studies the altered molecular mechanisms and the host-tumor interactions context (microenvironment and immunological milieu) and identifies biomarkers useful for early diagnosis, for the reduction of the risk of relapse or toxicity, for the choice of the most effective intervention.
For lung cancer, a molecular signature of a set of circulating miRNAs for early identification and assessment of aggressiveness is currently under clinical validation. This model is now being tested in other contexts, such as screening for colorectal cancer and active surveillance for prostate cancer.
The PC Program, endorsed by the Scientific Directorate, is acknowledged worldwide to have important expertise in managing active surveillance (AS) protocols. This observational option is being offered to patients with low and very low risk PC as an alternative to radical treatment since March 2005.
A promising miRNA signature, composed of 5 miRNA deregulated in the plasma samples of AS patients who experienced upgrading, has been identified and validated in order to improve the selection of AS patients: identification by multivariable detection rate and performance of the best one.
Analysis of samples from 1095 subjects who underwent colonoscopy in Hospitals joining the CRC screening program of the LHA of Milan, allowed the identification of miRNAs signature in plasma of individual at high risk for CRC.
INT is also involved in tertiary prevention studies. In particular, the DIET INT study, by intervention on lifestyle, aims at recurrency prevention and managing of side effects of head and neck cancer.

KEYWORDS

Diet and prevention
Biomarkers
Smoking cessation
Active surveillance

RARE TUMORS

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

OBJECTIVES

Rare cancers represents approximately one fourth of all cancers and are defined based on incidence (new cases/year) < 6/100,000.
Despite being a heterogeneous group of diseases (e.g. sarcomas, head and neck cancers, thymus epithelial tumours, neuroendocrine tumours) they share similar problems including lack of clinical expertise, issues in quality of care, and limitations in research.

The objectives of clinical and research activities on rare cancers include:

- centralization of rare cancer patients to dedicated reference centres through networking in order to reduce the health migration
- improve local control of the disease and overall survival of patients
- improve the knowledge on biology and natural history of rare cancers
- monitor the burden of rare cancers across EU MS and internationally
- support educational activities for improving rare cancer management
- development of guide lines "consensus-based" with the partnership of ESMO and ERNs

THEY SHARE SIMILAR PROBLEMS INCLUDING LACK OF CLINICAL EXPERTISE, ISSUES IN QUALITY OF CARE, AND LIMITATIONS IN RESEARCH

ACTIVITIES

- Teleconsultation at national (RTR- Rete Tumori Rari) and international level (ERN- European Reference Networks)
- Dedicated rare cancer patient pathway based on second opinion, muldisciplinary approach and networking
- Biological studies on profiling (genetic/molecular, immunological), in vitro and in vivo studies
- Development of predictive and prognostic tools
- National and international collaborative clinical trials
- National and international epidemiological studies based on cancer registries

- Partecipation of INT in 7 out of 10 domains of EURACAN (sarcoma, head and neck, NET, rare thoracic cancers, rare GYN, rare GU, rare GI) and the coordination of two of them (sarcoma and head and neck).

- Educational events in collaboration with ESO, ESMO e EURACAN.

OUTPUT

- Italian Rare Cancer Network officially established as reported in the Gazzetta Ufficiale

- Grant of the Ministry of Health 2016: "Italian Rare Cancer Network: Process monitoring and System impact Assessment"

- JARC (Joint Action on Rare Cancers): multi-stakeholder collaboration between 18 EU Countries and the European Commission, coordinated by INT, which will be pursued in a 3-year span (2016-2019) developed in order to guide, support and harmonize the work of the three ERNs focused on rare cancers (EuroBloodNet for rare haematological diseases; PaedCan for paediatric cancers; and EURACAN for adult solid rare cancers)

- ESMO-EURACAN for STS e GIST (in press on Ann Oncol)

- PDX models on rare histologies (solitary fibrous tumor, DD liposarcoma, epitheliod sarcoma)

- Demonstration of the efficacy of neoadjuvant chemotherapy in high risk extremity soft tissue sarcoma in a large randomized study (Lancet Oncol 2017;18:812-822)

- Development and validation of a nomogram to predict the risk of distant metastases and death of extremity soft tissue sarcoma (Lancet Oncol 2016;17:671-680) and development of an app (Sarculator) for friendly use in the clinic and research

- Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study Lancet Oncol 2017; 18: 1022–39)

- Online analysis tool for rare cancers (www.rarecarenet.eu)

KEYWORDS

Rare cancers
ERN
JARC

INNOVATION AND TECHNOLOGY: FOCUS ON SURGERY

FOCUS ON INTERDISCIPLINARY SELECTED RESEARCH AND CLINICAL PROGRAMMES

OBJECTIVES

Besides several improvements of medical treatments in oncology, radical surgical resection still represents the cornerstone of therapy for most solid tumors.
Modern oncologic surgery has evolved following three main pathways: conservative surgery, less invasive approaches and more accurate preoperative planning.
Each of these fields have achieved important advancements but still have to face several limitations.

Conservative surgery is feasible and safe for different kind of tumors (breast, lung, liver, ...) but its real adequacy often can be evaluated only at final pathological examination, i.e. several days after surgery.
Mini-invasive surgery offers a more rapid recovery and has undergone an important diffusion; the main limitation for its application is still the training of surgeons, which requires a longer learning curve. For what regards surgical planning CT and MRI ensure a high definition preoperative imaging, while during the operation is difficult to recognize the anatomical landmarks and the exact location of the tumor in the surgical field in order to obtain a radical resection.
The application of new technologies and augmented reality in the field of surgical oncology could help overcome the limitations described above.

CONSERVATIVE SURGERY, LESS INVASIVE APPROACHES AND MORE ACCURATE PREOPERATIVE PLANNING

ACTIVITIES

The commitment in the use emerging technologies is moving from laparoscopic surgery to the application of augmented reality approaches in surgical oncology.

Augmented reality assisted surgery utilizes technologies that superimpose a computer-generated image on the surgeon's view of the operative field, providing a composite view of the patient that includes anatomical information helpful for the surgeon. During surgery in fact, the eyes and hands of the surgeon remain the dominant 'imaging modalities' used to decide which tissues need to be resected and which tissues need to be preserved. Palpation and visual inspection are not always sufficient for discriminating between malignant and normal tissue types and

can lead to incomplete resections or the unnecessary removal of healthy tissue.
Hence, the possibility to see exactly the real extension of the tumor and its relationship with the surrounding structures is one of the most important unmet need in surgical oncology.
In this direction we are investigating the use of intraoperative imaging using invisible near-infrared fluorescent light to fill the gap between preoperative imaging and intraoperative reality.
Whereas visible light penetrates tissue on the micrometre scale, near-infrared light (700–900 nm) can travel millimetres—and up to centimetres—through blood and tissue.
This increased photon transport improves the identification of targets below the surface. This technology still has some limitations but it may become more useful with the development of selective fluorescent markers and more powerful detection systems.

OUTPUT

In the last two years laparoscopic surgery for tumors of the liver, pancreas and gastrointestinal tract has been adopted more and more frequently.

This has been possible because two new fully integrated operatory rooms and one new high definition (4K) laparoscope have been made available in our Institution. Patients operated through a minimally invasive approach reported better short term outcomes with a reduced length of hospitalization after surgery.
A dedicated room equipped with a workstation for video editing and a laparoscopic training simulator was set up, giving the opportunity to young surgeons to improve their skills in this particularly demanding area of surgery.

In the area of gastrointestinal surgery we are developing an augmented reality system aiming at a more precise, easy and fast surgery.
Particularly with the use of fluorescence we could improve the accuracy of the surgical act in different ways.
A fluorescent marker able to deposit in cancer cells can make the tumor visible during surgical resection in order to guide the correct plane of dissection. Other applications are sentinel node mapping, enhaced vision of vital structures and visualization of the vascularization of tissues.

KEYWORDS

Oncologic surgery
Laparoscopic surgery
Augmented reality
Near-infrared fluorescent imaging

SCIENTIFIC REPORT 2016-2017

DEPARTMENTS AND UNITS

SCIENTIFIC DIRECTORATE

The Scientific Directorate promotes and coordinates all scientific activities within the Foundation and manages the corresponding budget (around 25 M€ on yearly basis) with the support of a Technical-Scientific Committee (CTS) - as provided in the Statute of the Foundation – and with the assistance of the Scientific Directorate Board (CDS).

Since 2016, the Scientific Director initiated a process of reshaping the research area, its assessment mechanisms and advisory procedures in order to improve the quantity and quality of preclinical and clinical research, to strengthen programs for primary and secondary prevention and focus more strongly on orphan diseases.

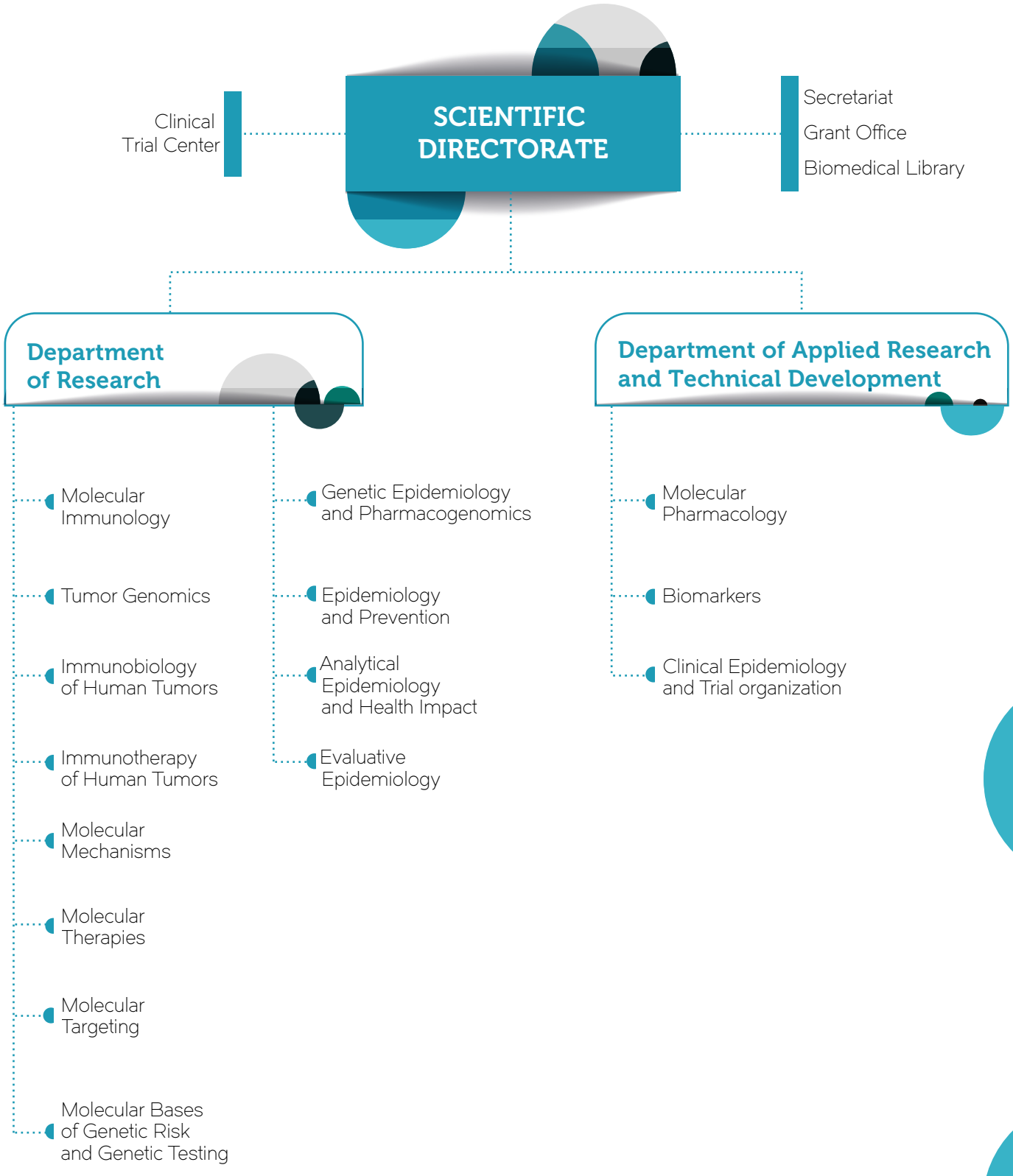
As a matter of facts, within the Strategic Research Plan 2016-2019 agreed upon by the Scientific and General Directors of the Institute, the creation of a research supporting structure was proposed. Thanks to its transparent and standardized mechanisms, this structure is able to bolster primarily and especially investigator-initiated studies (non-profit studies), both in the preparation of proposals (protocols) and in the implementation of the trials (statistical analysis, monitoring processes, insurance coverage, start-up funds, clinical trial center etc.).

Technologically advanced support to preclinical and clinical research involves platforms for molecular analysis, biobanks, animal testing facilities (research infrastructure), as well integrated mechanisms of scientific and political lobbying to attract funding from private agencies (industry) and the regional authorities.

The roadmap towards the new model is consistent with the changes required by the Strategic Organizational Plan (POAS - June 2018) whose implementation will extend to the end of 2019. As a result, the research area is now including one department dedicated to research activities (Research Department), and a second one, aimed at research support infrastructure and technological development (DRAST - Department for Applied Research and Technology Development). The aim of the latter infrastructure is to bridge the gap between preclinical and clinical research.

SCIENTIFIC DIRECTORATE

DEPARTMENTS AND UNITS



DEPARTMENT OF RESEARCH

DEPARTMENTS AND UNITS

MOLECULAR IMMUNOLOGY
Mario P. Colombo

TUMOR GENOMICS
Gabriella Sozzi

IMMUNOBIOLOGY OF HUMAN TUMORS
Andrea Anichini

IMMUNOTHERAPY OF HUMAN TUMORS
Licia Rivoltini

MOLECULAR MECHANISMS
Angela Greco

MOLECULAR THERAPIES
Delia Mezzanzanica

MOLECULAR TARGETING
Elda Tagliabue

MOLECULAR BASES OF GENETIC RISK AND GENETIC TESTING
Paolo Radice

GENETIC EPIDEMIOLOGY AND PHARMACOGENOMICS
Tommaso Dragani

EPIDEMIOLOGY AND PREVENTION
Vittorio Krogh

ANALYTICAL EPIDEMIOLOGY AND HEALTH IMPACT
Milena Sant

EVALUATIVE EPIDEMIOLOGY
Gemma Gatta

MOLECULAR IMMUNOLOGY

HEAD OF UNIT

Mario P. Colombo

RESEARCH ACTIVITY

The Unit studies the interplay between immune cells and the extracellular matrix (ECM) at site of tissue transformation.
The molecules involved in such cross-talk are expected to be early markers of tumorigenesis as well as responsible for tumor progression and potential target for new therapies. The focus is on immune cells endowed with immunosuppressive activities (i.e. myeloid cells, mast cells and regulatory T cells) and on two ECM proteins, SPARC and osteopontin, that play important roles in tissue homeostasis, wound healing and therefore cancer progression. The availability of genetically-engineered mouse models allows investigating the interplay between immune cells and ECM in tumor development and progression in mammary and prostate cancers and osteosarcoma. The Unit studies such interplay also in the specialized environments of primary (bone marrow) and secondary lymphoid organs, in relation to cancer-induced myeloproliferation and autoimmunity to lymphomagenesis transition.

HIGHLIGHTS

We dissected the regulatory interplay between components of the ECM and immune cells in solid tumors (breast and prostate cancers and osteosarcoma), with a particular focus on myeloid-derived suppressor cells and mast cells, and discovered that modulation of ECM exerts effects on immune cell infiltration, tumor histotype and response to immunomodulatory agents (*Sangaletti S, Cell Rep. 2016; Jachetti E, Mol Cancer Ther. 2017, Ratti C, Clin Cancer Res 2017; Chiodoni C, J. Leukoc Biol 2017; Sangaletti S, Cancer Immunol Immunother 2017; Sangaletti S, Curr Opin Pharmacol 2017*)

We discovered a new link between immune activation and changes in bone marrow microenvironment during the development and progression of myeloid malignancies, showing that persistent immune stimulation alters the bone marrow stroma architecture and the local tolerogenic microenvironment creating conditions favorable for myeloproliferation (*Tripodo C, Cancer Res 2017*)

KEYWORDS

Tumor microenvironment
Myeloid-Derived Suppressor Cells
Extracellular matrix
SPARC
Osteopontin
Mouse models
Bone marrow

TUMOR GENOMICS

HEAD OF UNIT

Gabriella Sozzi

RESEARCH ACTIVITY

Our research is focused on lung cancer, spanning from investigation of biomarkers for early detection to development of novel therapeutic strategies.

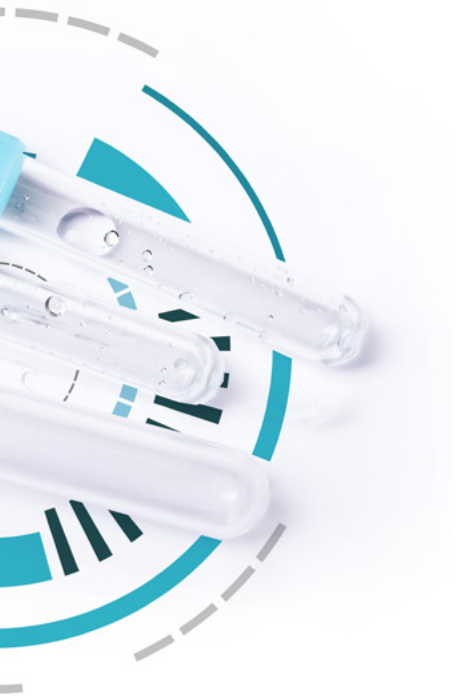
We have identified a three level risk classifier (MSC High, Intermediate and Low) based on 24 plasma miRNAs to be used as companion diagnostic in lung cancer CT-screening programs. It was possible to stratify CT-detected lung cancer cases according to MSC, mutation status and tumour stage into up to 5 groups with different clincial outcomes (5-year OS ranging from 8% to 100%). Analyses of MSC-miRNAs in various cell types and by in situ hybridization in lung tissues revealed a stromal and immune cells-related origin of most miRNAs, indicating potential influence of host factors in the modulation of lung cancer risk. We also used Patient-Derived Xenografts (PDX) to investigate the potential of innovative therapies based on modulation of the immune system and interference with the cross-talk between lung cancer (stem) cells and stromal cells.

HIGHLIGHTS

bioMILD trial.

In January 2016 the accrual of 4119 volunteers for the bioMILD lung cancer screening trial was successfully completed. At the end of 2017, 44% of enrolled volunteers had completed the study, reaching 3 years of follow-up. Overall, almost 8500 plasma MSC tests were performed and combined with corresponding Low Dose CT-imaging results.

Establishment of a large platform of Non Small Cell Lung Cancer (NSCLC) PDXs. Tumor samples from 97 patients were implanted in immunocompromised mice and 38 (≈40%) successfully gave rise to a PDX. An increased grafting was observed for tumors derived from patients with worse outcome, higher stage and higher $CD133^{+}/CXCR4^{+}/EpCAM^{-}$ stem cell content. Moreover, we observed that in almost two thirds of cases (63.2%), grafting was reached before clinical recurrence highlighting the potential utility of PDXs establishment as a functional testing of lung cancer aggressiveness and as a tool for personalized therapies *(Moro et al, Sci Rep 2017)*.



KEYWORDS

Lung Cancer
Genomics
Tumor Microenvironment.

IMMUNOBIOLOGY OF HUMAN TUMORS

HEAD OF UNIT

Andrea Anichini

RESEARCH ACTIVITY

The Unit has addressed major themes in the fields of solid tumor immunology and immunotherapy in collaboration with several clinical units in the Departments of Surgery, of Medical Oncology and of Pathology.
We focused the research efforts on:

- understanding mechanisms of development or impairment of adaptive anti-tumor immunity in solid tumors and deciphering factors contributing to response and resistance to immune checkpoint blockade;
- providing pre-clinical evidence for a feasible pharmacological approach to reverse cellular de-differentiation and to counteract immune escape mechanisms.

Major results:
evidence for inhibitory receptor+ T cells, retaining functional competence, in primary non small cell lung cancer (NSCLC) tissues has provided the rationale for anticipating immunotherapy to early stage of disease. In melanoma, we demonstrated that targeting of a single transcription factor can reverse de-differentiation and counteract immune escape.

HIGHLIGHTS

Immunotherapy in NSCLC stems from the principle that the tumor microenvironment contains only "exhausted" (functionally impaired) PD-1+ T cells needing to be rescued to effector function. In contrast, we found that early stage primary NSCLC lesions may contain tumor-specific PD-1+ T cells showing no evidence of defective anti-tumor function (Cancer Res 2017). The implication is that it becomes possible to test whether clinical benefit from immunotherapy is associated with presence of these functional effector T cells.
Immune escape mechanisms, as loss of expression of immunogenic T cell epitopes, represent a major hurdle for efficacy of immunotherapy. By investigating the role of the transcription factor NFATc2, constitutively expressed in a subset of melanomas, we found that its pharmacological targeting can rescue expression of antigens recognized by tumor-specific T cells (Oncogene 2016), thus providing pre-clinical evidence for an effective strategy to counteract immune escape.

KEYWORDS

Tumor immunity
Immunotherapy
Solid tumors

IMMUNOTHERAPY OF HUMAN TUMORS

HEAD OF UNIT

Licia Rivoltini

RESEARCH ACTIVITY

Identification of immune-based tools for patients' selection and treatment combinations in melanoma and HCC.

Through standardized multiparametric immune profiling (including multicolor cytofluorimetry, cyto/chemokine secretome and gene expression profile of PBMC and tumor lesions), we identified a key role of metabolic pathways involving pH regulations and the cross-talk with immunosuppressive myeloid cell components. In vitro models of myeloid immunosuppression have been created for large-scale screening of modulating drugs (Horizon 2020 Precious project). Immunomodulation through life style changes is also been tested in healthy volunteers as preparatory to clinical trials to be performed in early melanoma and breast cancer patients (TRANSCAN - DigesT project and AIRC-AGILITY trial).

HIGHLIGHTS

Identification and validation of a peripheral blood Myeloid Index Score predicting rapid progression and resistance to therapy in melanoma patients, with evidence about the role of chemotherapy as a preconditioning regimen to reduce myeloid-mediate immunosuppression. Discovery of the molecular patterns governing tumor-mediated myeloid conversion into immunosuppressive effectors (MDSC), and identification of a myeloid miR signature inducing MDSC in vitro and predicting resistance to immunotherapy when tested in baseline plasma samples of melanoma patients undergoing immune checkpoint inhibitors.

KEYWORDS

Tumor Immune Escape
Immune metabolism
Myeloid-Derived Supressor Cells
pH regulators

MOLECULAR MECHANISMS

HEAD OF UNIT

Angela Greco

RESEARCH ACTIVITY

The activity of the Unit involves two main topics.

Identification and validation of molecular mechanisms contributing to thyroid carcinogenesis.

The final goal is the identification of markers for detection, prognosis, follow up, and of novel therapeutic targets. Relevant results include: characterization of thyroid tumor cell vulnerability; dissection of thyroid tumor cells and macrophage cross-talk; identification and functional characterization of miRNA under-expressed in thyroid carcinoma; identification of miRNAs over-expressed in thyroid tumor cells and over-represented in plasma, to identify circulating miRNAs with prognostic value.

Proteomics-based approaches are applied in the contest of cellular and molecular biochemistry and clinical science.

Studies were performed to investigate the role of iron metabolism in breast cancer cells, of MIF/CD74 axis in colon carcinomatosis and identify biomarkers in cerebrospinal fluid from children with central nervous system tumors.

HIGHLIGHTS

Thyroid carcinoma

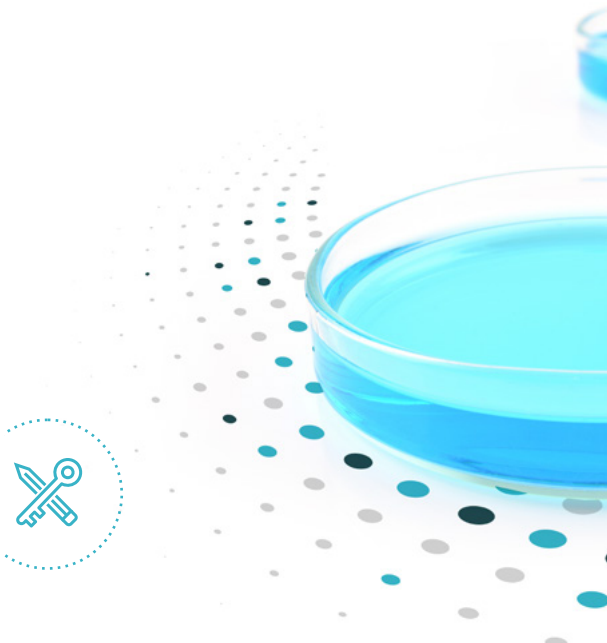
- COPZ1 and MASTL, two genes previously identified as thyroid tumor cell vulnerability, were validated as novel therapeutic targets; their inhibition affects thyroid tumor cell viability through mechanisms partially dissected.
- miR-451 was identified as under-expressed in Papillary Thyroid Carcinomas (PTC) and shown to act as an oncosuppressor. Moreover, lower expression of miR-451a correlates with aggressive clinical-pathological features of PTC.
- miR-375, the most over-expressed miR in medullary thyroid cancer (MTC), was identified as circulating miRNA, and evaluated as a novel prognostic marker in metastatic MTC patients.

Pediatric tumors

A multimethod approach using nanoparticles, mass spectrometry and statistical was used to identify low-abundance proteins in cerebrospinal fluid from children with central nervous system, indicative of tumor metastatic spread.

KEYWORDS

Thyroid tumors
miRNA
Tumor cell vulnerability
Mass spectrometry
Clinical proteomics
Cell biology
Cell signaling
Iron metabolism



MOLECULAR THERAPIES

HEAD OF UNIT

Delia Mezzanzanica

RESEARCH ACTIVITY

The Unit is involved in translational research dedicated to respond to the unmet clinical needs of ovarian cancer: late diagnosis, rapid progression, frequent relapse and development of chemoresistance.

The collaboration with surgery and pathology departments and with the functional genomics, allows the achievement of important steps further in understanding the molecular basis of tumor progression and disease recurrence. By using 3D models of patient-derived cells we deciphered signal transduction mediated by adhesion molecules and microenvironment interaction. By integrating patients' clinical data with data derived from multiple level of analysis (gene/miRNA expression, methylation, exome sequencing and metabolome) we deciphered the regulatory networks related to drug sensitivity/cellular plasticity. By antibody engineering we developed antibody-based diagnostic/therapeutic tools, to be tested in short term patients' derived cultures and patented for clinical application.

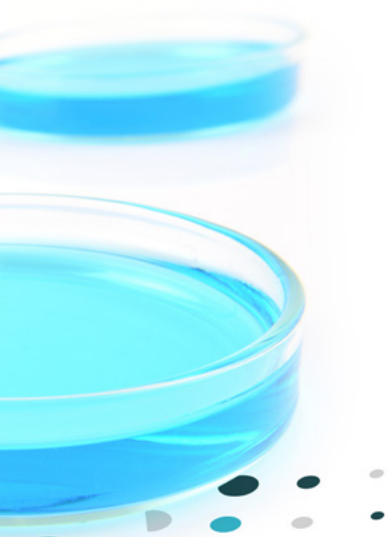
HIGHLIGHTS

We derived a miRNA-based predictor of ovarian cancer risk of relapse named MiROvaR.

Its applicability as a useful clinical-grade assay has been proposed to identify ovarian cancer patients at higher risk in two clinical settings: late stage patients, candidate to more aggressive strategies; early stage patients who really need chemotherapy thus reducing overtreatment of low risk patients.

We defined E-cadherin, the cell-cell adhesion molecule, as a tumor enhancer that positively contributes to growth signaling due to loss of PLEKHA7, a determinant of cell polarity in epithelial tissues that clinically emerges as a possible marker for less aggressive ovarian cancer.

We produced human antibody fragments in different formats, recognizing the alpha-Folate Receptor and PSMA, whose variable regions have been patented. The antibody fragments have been proposed for tumor imaging and treatment and for CARs and bispecific antibody construction for T cells redirection against tumor cells.



KEYWORDS

Ovarian cancer
Tumor progression
Antibody engineering

MOLECULAR TARGETING

HEAD OF UNIT

Elda Tagliabue

RESEARCH ACTIVITY

Our research aim is to dissect the intrinsic properties of breast carcinoma cells and the host-related changes accompanying tumor development, progression and response to therapy as an avenue toward enhancing cure rate.
The research topics focused on:

Intrinsic properties of breast cancer cells relevant to tumor development and progression.
We provided evidences that d16HER2 variant constitutes an important HER2 isoform that sustains the expansion of cancer stem cells;

Interactions between tumor and stromal cells that sustain breast cancer cells growth and invasiveness.
We discovered that tumor-derived exosome-associated microRNAs, when uptaken in endothelial cells, disrupt endothelial barrier and cause tumor cell transmigration;

Development and validation of new diagnostic strategies.
We described new markers for breast cancer early diagnosis consisting of circulating extracellular matrix components and small peptides originating from host/tumor interaction.

HIGHLIGHTS

HER2 proteome in breast carcinoma progression and response to therapy.
Whole-transcriptome analysis of human HER2-positive breast carcinomas and transgenic mouse models resembling these tumors provided evidences that d16HER2 splice variant constitutes an important isoform that sustains cancer stem cell expansion. Tumors expressing high levels of activated d16HER2 show the greatest benefit from Trastuzumab, supporting the notion that in these tumors Trastuzumab targets cancer stem cells affecting tumor progression *(Castagnoli et al., Oncogene)* .

Host-related changes accompanying tumor progression.
We found that triple-negative breast cancer cells actively release exosomes containing miR-939 that when taken up by endothelial cells causes a decrease of VE-cadherin expression. Loss of cell-to-cell contact and the disruption of endothelial barrier favor cancer cells transmigration *(Di Modica et al., Cancer Lett, 2017)*.

KEYWORDS

Breast cancer
Tumor microenvironment
Targeted therapy

MOLECULAR BASES OF GENETIC RISK AND GENETIC TESTING

HEAD OF UNIT

Paolo Radice

RESEARCH ACTIVITY

The activities of this unit are focused on the identification and characterization of genetic elements associated with hereditary predisposition to cancer and cancer progression. Our studies are focused on familial breast/ovarian carcinoma (HBOC) and Wilms tumor (WT). As concerned HBOC, our research is primarily oriented to the assessment of the clinical relevance of variants of uncertain significance (VUS) in BRCA1 and BRCA2, the genes most frequently associated with this hereditary condition. The goal is to increase the informativeness of genetic testing in high-risk families, offering risk-reduction options to a larger number of individuals.
WT is the most frequent childhood renal cancer with a survival rate >90%. However, only half of children who suffer from tumour relapse reach durable remission. Our studies aim to identify genetic/epigenetic markers associated with WT recurrence, in order to select patients eligible to more aggressive treatments impacting on their survival.

HIGHLIGHTS

Risk-related relevance of a BRCA2 variant affecting mRNA splicing: a model for clinical calibration of spliceogenicity.

We performed a case-control analysis and quantified BRCA2 isoforms retaining or missing exon 3 in carriers of the c.68-7T>A variant and wild-type controls. The probability of pathogenicity of the variant was $7.44 \times 10e^{-115}$ and its associated exon 3 exclusion rate was 20%. Genetic and quantitative transcript analyses together inform the threshold for the ratio between functional and altered BRCA2 isoforms compatible with normal cell function.

Development and validation of a functional assay for the clinical classification of variants in BRCA genes.

We applied an in vitro reassembly assay for the study of protein-protein interactions to evaluate VUS in BRCA genes. Our results suggest that this assay is a robust, fast and cheap method to identify mutations affecting protein functioning and contribute to the definition of the clinical significance of VUS.

KEYWORDS

Hereditary breast/ovarian cancer
BRCA genes
Variants of uncertain significance
Wilms tumour
Tumor recurrence
Prognostic markers

GENETIC EPIDEMIOLOGY AND PHARMACOGENOMICS

HEAD OF UNIT

Tommaso Dragani

RESEARCH ACTIVITY

In an experimental model, we depicted the architecture of germline control of gene expression in mouse lung cancer, highlighting the importance of the Pas1 locus as a tumor-modifier locus.
In a RNA-Seq study on non-involved lung tissue of surgically treated lung adenocarcinoma patients, we found the presence of read-through transcripts in apparently normal lung tissue, with inter-individual differences in patterns and abundance. We also found their down-regulation in tumors, suggesting that these chimeric transcripts may function as tumor suppressors in lung tissue.
In a replication study, we found that eight single nucleotide polymorphisms (SNPs) associated with lung adenocarcinoma risk and three associated with survival. Five of these SNPs acted as expression quantitative trait loci (eQTLs), suggesting that these SNPs exert their effects on cancer risk/outcome through the modulation of mRNA levels of their target genes.

HIGHLIGHTS

Read-through transcripts are down-regulated in lung adenocarcinoma.
Read-through transcripts result from the continuous transcription of adjacent, similarly oriented genes, with the splicing out of the intergenic region. We found their presence in apparently normal lung tissue, and their down-regulation in lung adenocarcinoma, suggesting that these chimeric transcripts may function as tumor suppressors in lung tissue.

Functional assessment of genetic susceptibility variants for lung cancer as expression quantitative trait loci.
Several single nucleotide polymorphisms (SNPs) associated with risk of prognosis of lung cancer, act as expression quantitative trait loci (eQTLs), suggesting that their mechanisms of action on cancer risk/outcome involve the modulation of mRNA levels of their target genes.

KEYWORDS

Complex genetics
Precision medicine
Germline polymorphisms

EPIDEMIOLOGY AND PREVENTION

HEAD OF UNIT

Vittorio Krogh

RESEARCH ACTIVITY

The Unit is involved in large prospective studies on the association between diet, hormones, nutrition, lifestyle, genetic factors, and cancer risk: EPIC (European Prospective Investigation into Cancer and Nutrition); ORDET (hORmones and Diet in the Etiology of breast Tumor); TPM, that evaluates the prognostic role of androgens and related endocrine-metabolic factors in breast cancer.
The Unit is also involved in many randomized controlled trials (RCT): COS, a RCT of diet and physical activity in BRCA mutation carriers; TEVERE, a blinded RCT of diet and metformin for primary prevention of breast cancer; MeMeMe, a RCT of diet and metformin for primary prevention of age-related chronic diseases; DIANA-5, a multicentric RCT of a diet based on Mediterranean and macrobiotic recipes and principles, and moderate physical activity, in reducing additional breast cancer events in women with early stage invasive breast cancer at high risk of recurrence because of metabolic or endocrine milieu.

HIGHLIGHTS

The main results of prospective published studies are the following: plasma riboflavin and vitamin B-6 are inversely associated with increased breast cancer (BC) risk; among postmenopausal women, high CRP was significantly associated with increased BC risk, and high adiponectin with significantly reduced BC risk, among premenopausal women, high TNF-α and IL-6 were associated with BC increased risk, and high leptin with reduced risk.
High glycaemic index was associated with increased colon and bladder cancer risk; high glycaemic load was associated with increased colon and diabetes-related cancers and decreased rectal cancer risk. Blood and nail selenium concentrations are associated with a reduced risk of aggressive prostate cancer.
In the COS RCT, women in the intervention group significantly reduced body weight, BMI, fat mass, hip circumferences, total cholesterol and triglycerides compared to the control group.

KEYWORDS

Diet
Hormones
Metformin

ANALYTICAL EPIDEMIOLOGY AND HEALTH IMPACT

HEAD OF UNIT

Milena Sant

RESEARCH ACTIVITY

EUROCARE

We finalized studies on survival by stage at diagnosis, pancreatic cancer trends and CML long-term survival. The 6th round is on-going (patients diagnosed 2009-2013).

The HIGH RESOLUTION (HR)

database includes 45376 breast, colorectal, lung cancers, melanoma and lymphoma patients diagnosed in 2009-2014 (53 cancer registries, 13 countries). We centralise, manage and analyse data via the website www.hrstudies.eu. Follow-up will be updated, new neoplasms will be included.

INT CANCER REGISTRIES

The breast cancer registry (RTM) is up and running, it includes 5164 primary breast cancers and regularly contributes data to various studies; follow-up is under study. The pancreatic cancers registry (RTPC), based on RTM methods, contributed to EUROCAN-Platform. Algorithms for registering lung and colorectal cancers were developed for specific studies. As in past EU Joint Actions on Cancer, we contributed to plan the new one (IPAAC) co-leading a WP on Cancer Information and Registries.

HIGHLIGHTS

EUROCARE and HR

Variation in stage at diagnosis only partially explains survival inequalities across areas and patient groups; in Eastern EU, poor stage-specific survival suggests less effective care, likely because fewer resources are allocated to health care than in other countries.Varying adhesion to clinical guidelines and patterns of care contribute to survival inequalities. In Italy, BC patients of low-socio economic status have more relapses and are significantly less likely to receive standard care compared to whealthy ones.

RTM and RTPC

RTM and RTPC are almost entirely based on automatic data-capturing from institutional files (e.g. pathology, pharmaceutic, SDO) and allow researchers and clinicians to quickly identify cases of interest, with predefined demographic and standardized clinical-pathological variables. RTM is connected with the blood bank and the blood exams database. Published studies proved these registries are useful for clinical, biological and outcomes research.

KEYWORDS

Cancer outcomes
Registries
Survival
Care
Comorbidity

EVALUATIVE EPIDEMIOLOGY

HEAD OF UNIT

Gemma Gatta

RESEARCH ACTIVITY

Evauative and descriptive epidemiology on:

- rare cancers
- cancers in children, adolescents and young adults
- estimation of the risk of dying in cured from cancer patients
- population-based comparative cancer survival studies

For the above topics the Unit received funds from the EC, the Ministry of Health and the NCI (Bethesda, US). Currently, this Unit is strongly involved in the European Joint Action of Rare Cancers (JARC). Furthermore, a three years project (ADA) on adolescents and young adults with cancer is supported by institutional funds (5x1000) and a collaborative project on rare cancers for the harmonization of the definition and list of rare cancers is on going with the NCI.

HIGHLIGHTS

European Joint Action on Rare Cancer

we are in the coordination WP and in leader of the WP4. JARC is supported by the Chafea – 3rd Health Programme (Europa). This is the first Joint European on rare cancers which will support the activities of the European Reference Network. JARC is the result of two previous EU project on rare cancers which estimated for the first time in Europe the burden of rare cancers and created a rare cancers informative network on rare cancers among different stakeholders.

ADA project

Adolescents and young adults with cancers in Italy. How to ensure access to the best care and quality of survival. This is a unic national project on this special group of patients which is realised in close connection with clinicians.

KEYWORDS

Adolescents and young adults (AYA)
Rare cancer
Cancer Survival
Real world data

DEPARTMENT OF APPLIED RESARCH AND TECHNICAL DEVELOPMENT

BIOMARKERS

Maria Grazia Daidone

MOLECULAR PHARMACOLOGY

Nadia Zaffaroni

CLINICAL EPIDEMIOLOGY AND TRIAL ORGANIZATION

Luigi Mariani

BIOMARKERS

APPLIED RESARCH AND TECHNICAL DEVELOPMENT

HEAD OF UNIT

Maria Grazia Daidone

RESEARCH ACTIVITY

The activity of the Unit has been addressed to identify and validate cancer-related actionable biomarkers relevant for disease progression and treatment response by integrating cell biology and molecular approaches, high-throughput techniques and bioinformatics tools.

In the last 2 years we focused on liquid biopsy, which allow capturing tumor's genomic landscape, tracing disease evolution and likely overcoming tumor heterogeneity-related constraints by a non-invasive approach. In this context, we:

- investigated the predictive role of circulating microRNA (ct-miRNA) in plasma from HER2+ breast cancer (BC) patients enrolled in a multicentric trial of anti-HER2 therapy;
- assessed the feasibility of detecting circulating tumor DNA (ctDNA) in plasma of women with early stage BC;
- developed a pipeline for improved enrichment/identification/molecular analysis of CTC at single cell level, applicable to different solid tumors.

HIGHLIGHTS

ct-miRNAs discriminate patients with/without pCR to HER2-targeted therapy in the NeoALTTO trial. In particular, ct-miRNAs appear to be relevant for early identification (after 2 weeks of neo-adjuvant treatment) of patients responsive to trastuzumab for whom combination with other HER2-targeted therapy does not appear justified. ct-miRNA evaluation appears as a promising tool for exploring de-escalating strategies.

A newly developed CTC-protocol allows CTC detection in 80-100% of cholangiocarcinoma patients, with a distinct phenotype (epithelial vs non conventional) according to tumor location (intra or extra-hepatic). The potential of CTC as a tissue biopsy surrogate is under study (*Adv Exp Med Biol. 2017;994:83-103*).

Activation of a prospective study in patients with early stage triple negative BC (90 cases have been already recruited) to assess whether ctDNA post-surgical screening can detect minimal residual disease and/or anticipate relapse.

KEYWORDS

Solid tumors
Liquid biopsy
ctDNA
CTC
microRNA

MOLECULAR PHARMACOLOGY

APPLIED RESARCH AND TECHNICAL DEVELOPMENT

HEAD OF UNIT

Nadia Zaffaroni

RESEARCH ACTIVITY

The preclinical activities are mainly related to the following issues:

- identification and validation of novel therapeutic targets,
- characterization of inherent and acquired drug-resistance mechanisms and their relationship with the metastatic phenotype,
- development of rationally designed therapeutic combinations and optimization of their delivery through the use of nanodevices,
- development and characterization of preclinical models of rare diseases (specific soft-tissue sarcoma histologies, peritoneal mesothelioma, etc).

As far as clinical-related activities are concerned, a comprehensive molecular characterization of low/very-low risk prostate cancers is ongoing with the aim to identify tissue (DNA, proteins) and circulating (microRNAs, DNA, proteins) biomarkers to improve the criteria for inclusion of patients in active surveillance protocols.

HIGHLIGHTS

Identification and validation of miRNAs as novel therapeutic targets:

through the search for miRNAs differentially expressed in tumors and the assessment of their biological functions, we identified i) miR-380-5p as an inhibitor of telomerase-mediated tumor cell immortalization and miR-34a as a negative regulator of c-MET and AXL-mediated cell growth and invasion in peritoneal mesothelioma, and ii) miR-875-5p as an enhancer of radiation response of prostate cancer through EGFR-ZEB1 axis repression.

Development of novel in vivo models of rare sarcomas:

we developed and characterized PDXs of solitary fibrous tumor and epitheliod sarcoma, two histologies for which preclinical models are currently unavailable, and i) demonstrated the reliability of the models by comparing the effect of a variety of chemotherapeutic agents with clinical results, and ii) according to the molecular profile of the models, showed the activity of epigenetic modulators, such as the EZH2 inhibitor tazemetostat.

KEYWORDS

Therapeutic targets
Drug-resistance
Nanodelivery systems
Novel preclinical models
Biomarkers of risk

CLINICAL EPIDEMIOLOGY AND TRIAL ORGANIZATION

APPLIED RESARCH AND TECHNICAL DEVELOPMENT

HEAD OF UNIT

Luigi Mariani

RESEARCH ACTIVITY

The Unit provides statistical support in relation to the design and assesment of results of clinical trials, observational and population-based studies, mainly in the areas of surgical, medical or hematological oncology.
The above activity benefits from the experience and staff expertise in biostatistics, informatics and biomedicine. By taking into account the developments of statistical methodology in many areas of current interest (like early study design, event history analysis, quality of life and pharmacœconomic evaluation tools), the Unit strives to put into practice the most updated methodologies suitable for design and analysis of diagnostic, therapeutic, chemoprevention and prognostic trials.

HIGHLIGHTS

Original statistical models were developed and validated to predict overall survival and occurrence of distant metastases in the context of soft-tissue sarcomas of the extremities and urothelial carcinoma receiving first-line platinum-based chemotherapy. International series of respectively 3752 and 1020 patients were employed, and nomograms were built in order to improve clinician's abilities to assess patient prognosis, strengthen the prognosis-based decision making, enhance patient stratification, and inform patients in the clinic.
In the field of therapeutic trials, an easy-to-use statistical tool based on Bayesian predictive probability calculation was presented for the design and analysis of biomarker-based, early-phase, noncomparative trials. Scenarios like this are likely to arise in future trials on immune checkpoint inhibitors for which application of formal yet manageable and efficient methods might better support the therapeutic development process.

KEYWORDS

Clinical epidemiology
Statistics
Survival analysis

DEPARTMENT OF CRITICAL AND SUPPORTIVE CARE

DEPARTMENTS AND UNITS

ANESTHESIA AND INTENSIVE CARE

Martin Langer
Franco Valenza

PALLIATIVE CARE, PAIN THERAPY AND REHABILITATION

Augusto T. Caraceni

CARDIOLOGY

Carlo Materazzo
Fabio Turazza

CLINICAL NUTRITION

Cecilia Gavazzi

PULMONOLOGY

Roberto Boffi

CLINICAL PSYCHOLOGY

Claudia Borreani

ANESTHESIA AND INTENSIVE CARE

HEAD OF UNIT

Martin Langer
Franco Valenza

CLINICAL AND RESEARCH ACTIVITY

The anesthesia program at INT includes a number of sub-specialties, among which colorectal, hepato-bilio-pancreatic (inclusive of liver transplantation), thoracic, otolaryngo-head and neck, breast, gynecolocic, urologic, melanoma and sarcoma cases, for a total of more than 8000 procedures per year.
A dedicated acute pain service is active, accounting for the care of 650 peridural catheters and 1500 patient controlled analgesia per year. Twelve beds of immediate post anesthesia care and 6 beds of intensive care (ICU) serve the peri-operative treatment of the numerous fragile adult and pediatric subjects undergoing surgery at INT. Every year anesthesia is delivered for more than 700 diagnostic or therapeutic procedures out of the operating room, and 850 long-mid term vascular catheters are positioned. ICU staff also provides in hospital rapid response to acute critical ilness, including 150 medical ICU admissions.
Research activity among the anesthesia and ICU staff at INT is part of the daily routine. The staff is involved in several research projects, either in the role of coordinators, or as part of multidisciplinar collaborations.

HIGHLIGHTS

A number of investigations are underway, including the coordination of a multicenter randomized controlled trial on the role of neuromuscular blockade agents in thoracic surgery, the study of coagulation deragements occuring during complex surgical procedures (hyperthermic intraperitoneal chemotherapy - liver transplantation), the role of perioperative pain on chronic post-thoracotomic pain, and thrombosis surveillance in mid-long term catheterization.
Recently, an interest has been developed on the pre-surgical role of nutrition and exercise as a mean of improving perioperative outcome.

KEYWORDS

Anaesthesia
Critically ill
Pain

PALLIATIVE CARE, PAIN THERAPY AND REHABILITATION

CRITICAL AND SUPPORTIVE CARE

HEAD OF UNIT

Augusto T. Caraceni

CLINICAL AND RESEARCH ACTIVITY

The unit provides comprehensive specialized care for patients with advanced cancer and for cancer survivors.
In particular, it offers specialized outpatient care for pain and other symptoms related to cancer and oncological treatments, a palliative care service for patients admitted in INT, admission to hospice for end of life care and a home care program for those wishing to stay at home during the last period of their life. The unit provides full range of rehabilitation interventions with focus on chronic lymphedema, pelvic floor rehabilitation, pain and disability following surgery and/or antineoplastic treatments.
Clinical research, associated to the clinical program, focuses on pain management, symptom control and rehabilitation, opioid pharmacogenetics and variability of pain and analgesia, integration of palliative and oncology care, end-of-life care strategies and outcomes.

HIGHLIGHTS

Studies on cancer pain and analgesic interventions are aiming at personalizing pain assessment and treatment.

The "MOLO 13 study" aims at confirming preliminary results on the contribution of genetic and clinical variability to opioid analgesia and side effects in a population of cancer patients with pain treated with strong opioids. Recently, an association between nucletide polymorphisms and susceptibility to opioid induced nausea and vomiting was identified.

The comparison of sublingual fentanyl and subcutaneous morphine for breakthrough cancer pain was assessed and quantified in a non-inferiority placebo controlled clinical trial.

Participation to the palliative radiotherapy and inflammation study (PRAIS) (www.ntnu.edu/prc/prais-study-presentation), which is a prospective multcenter internatonal study that investigates the existance of possible clinical and biomarker predictors of pain reduction response to palliative radiotherapy for bone cancer pain.

KEYWORDS

Palliative care
Pain
Symptoms control
Quality of life
Rehabilitation

CARDIOLOGY

HEAD OF UNIT

Carlo Materazzo
Fabio Turazza

CLINICAL AND RESEARCH ACTIVITY

The Cardiology Unit carries out cardiac evaluation of patients undergoing surgical interventions or chemoradiotherapy for cancer in order to define individual cardiovascular risk and predict the need of monitoring complications.

Patients candidates for surgery and/ or medical therapy, are subjected to diagnostic tests and therapies for ischemic heart disease, hypertension, valvular heart disease, arrhythmias, and congestive heart failure before and/or during the course of their cancer treatment.
Preoperative evaluation of cardiac risk, perioperative assessment and monitoring are performed according to the latest International Guidelines.

Regular cardiologic surveillance to assess the cardiotoxicity of new experimental drugs is carried out for all ongoing Phase I, II, and III clinical studies (monoclonal antibodies, receptor tyrosine kinase inhibitors, BRAF inhibitors, MEK inhibitors).

The Cardiology Unit has been involved in over 200 clinical trials for the monitoring of cardiovascular toxicity related to anti-neoplastic treatments, in collaboration with other clinical Units of INT.

KEYWORDS

Cardiotoxicity
Cardiologic assessment

CLINICAL NUTRITION

HEAD OF UNIT

Cecilia Gavazzi

CLINICAL AND RESEARCH ACTIVITY

The goal of the unit is the treatment of malnutrition and sarcopenia in order to improve tolerance and response to cancer therapy and quality of life.
All patients at high risk for malnutrition are included in a personalized nutrition support programme which includes: body composition evaluation, nutritional counseling and artificial nutrition. About 350 patients/year are included in a nutrition programme at oncological diagnosis and 100 patients/year are supported with home artificial nutrition during the entire oncologic treatment, successfully maintaining a good nutritional status and an acceptable quality of life.
Regarding the research activity, the unit is involved with the development of algorithms for correct nutrition programming of patients with cancer undergoing different treatments, with a focus on upper gastro-intestinal cancer and the identification of the best methods for the evaluation and monitoring of nutritional status and body composition.

HIGHLIGHTS

Algorithms were developed for correct nutrition support in different stages of gastric cancer.
They were included in several publications and in the guidelines of the Italian Association of Medical Oncology (AIOM).

The use of CT imaging for the evaluation and monitoring of body composition and skeletal muscle index was developed and introduced in several research protocols.

KEYWORDS

Malnutrition
Nutritional status
Body composition

PULMONOLOGY

CRITICAL AND SUPPORTIVE CARE

HEAD OF UNIT

Roberto Boffi

CLINICAL AND RESEARCH ACTIVITY

The most important activity is the clinical evaluation of patients with lung and thoracic tumors who are candidates for thoracotomy and/or pulmonary resection, aimed to assess the risk of postoperative morbidity and mortality.
The evaluation of respiratory conditions is based on the spirometric examination, for the study of static and dynamic pulmonary volumes, on the plethysmographic examination for the evaluation of the resistances and conductances of the airways and the diffusing capacity of the lungs for carbon monoxide. High risk patients are also subjected to a cardio-respiratory ergometric test.
Another activity concerns the monitoring of pulmonary function in patients subjected to chemotherapy, radiotherapy, target therapy and combined treatments whose potential lung toxicity is known.
An important space is dedicated to diagnostic-therapeutic activity of chronic obstructive pulmonary diseases and, more generally, of pulmonary complications related to cigagarette smoking.

HIGHLIGHTS

In the unit there is one of the biggest anti-smoking centers in Italy.
Major achievements that led to manuscript publications were the measurements of the quantity and quality of particulate matter and volatile organic compounds emitted by e-cigarettes, the identification of genetic polymorphisms related to the possible response to antitabagic treatments in smokers, and the data collection of smoking cessation of hospitalized patients.
Participationt to the European Horizon 2020 project "TackSHS" (http://tackshs.eu/), aimed to tackle secondhand tobacco smoke and e-cigarette emissions (exposure assessment, novel interventions, impact on lung diseases and economic burden in diverse European populations).

KEYWORDS

Lung cancer
Chronic obstructive pulmonary disease (COPD)
Smoking cessation
Environmental tobacco smoke
electronic cigarettes

CLINICAL PSYCHOLOGY

HEAD OF UNIT

Claudia Borreani

CLINICAL AND RESEARCH ACTIVITY

Clinical activity of the unit aims at enhancing quality of life and well-being of people facing cancer.
Depending on the level of psychological suffering, a psychological plan is created to support the patient and possibly relatives or any other people who may be affected by the difficult situation.This is accomplished by providing expert clinical intervention such as individual psychological counselling, short psychotherapies, verbal and psycho-bodily groups, psycho-educational groups and family therapies. The Clinical Psychology Unit also provides staff support, psychological supervision and psychological training for health care providers. Multidisciplinary clinical projects, specifically addressed to support cancer patients undergoing liver transplantation or to support clinical decision making in patients with BRCA1-BRCA2 gene mutations, are also carried out. The psycho-oncological research is concerned with the psychological, social, behavioural and ethical aspects of cancer.

HIGHLIGHTS

The psychological consequences after adjuvant aromatase inhibitor therapy in breast cancer women
The study shows a slight deterioration in quality of life scores and a general increase in psychological symptoms during the first six month of adjuvant aromatase inhibitor therapy.

Fear of cancer recurrence in disease free adult hematological patients
The study analyzes the prevalence of fear of cancer recurrence in a sample of adult hematological patients free from disease and investigates the association of fear of cancer with quality of life and demographic, medical and psychosocial factors.

KEYWORDS

Quality of life
Psychological wellbeing
Staff support

SURGERY DEPARTMENT

DEPARTMENTS AND UNITS

GASTROINTESTINAL AND HEPATOPANCREATOBILIARY SURGERY. LIVER TRANSPLANTATION.

Vincenzo Mazzaferro

COLORECTAL SURGERY

Ermanno Leo

BREAST SURGERY

Secondo Folli

PLASTIC SURGERY

Umberto Cortinovis

MELANOMA AND SARCOMA

Mario Santinami

DIAGNOSTIC AND THERAPEUTIC ENDOSCOPY

Enzo Masci

PEDIATRIC SURGERY

Luigi Piva

OTORHINOLARYNGOLOGY, MAXILLOFACIAL AND THYROID SURGERY

Cesare Piazza

GYNECOLOGIC ONCOLOGY

Francesco Raspagliesi

THORACIC SURGERY

Ugo Pastorino

UROLOGIC SURGERY

Roberto Salvioni

LASER THERAPY

Anna Colombetti

DAY SURGERY

Aldo E. Bono

GASTROINTESTINAL AND HEPATOPANCREATOBILIARY SURGERY. LIVER TRANSPLANTATION

HEAD OF UNIT

Vincenzo Mazzaferro

CLINICAL AND RESEARCH ACTIVITY

Our clinical activity is focused on treating gastrointestinal tract, pancreatic, localized and metastatic liver and neuroendocrine (NET) tumours, hospitalizing about 800 patients per year.
A program of liver transplantation for hepatocellular carcinoma (HCC) and other indications is active, with almost 700 transplantations to date. The Unit is a referral point for CCR metastases and HCC, providing a wide range of therapeutic strategies including surgery, TACE, RF ablative techniques (percutaneous/laparoscopic), and Y90 TARE for non-surgical HCC or as a bridge to liver transplantation. As experienced in laparoscopic GI surgery, our Unit is part of the IGoMils study for the evaluation of outcomes of mininvasive approach to the liver. Patients affected by hepatic metastases from colorectal tumours are treated through tailored strategies including liver-first, colon-first, combined surgery or staged hepatectomies. The Unit is certified by the European Neuroendocrine Tumor Society (ENETS).

HIGHLIGHTS

Metroticket Project 2.0:
model based on level of AFP, tumor size, and tumor number, to determine risk of death from HCC-related factors after LT to be used to select end points and refine selection criteria for liver transplantation in HCC.

KEYWORDS

Liver surgery
Liver transplantation
Gastric surgery
Pancreatic surgery
Neuroendocrine tumors
Hepatocellular carcinoma
Cholangiocarcinoma
Liver metastasis
Radioembolization

COLORECTAL SURGERY

HEAD OF UNIT

Ermanno Leo

CLINICAL AND RESEARCH ACTIVITY

The Unit is a recognized European referral center for colorectal tumors.
The case load of colorectal surgeries is about 600 per year.
Our Unit is chiefly focused on distal rectum tumors.

High standards of care for the management of these patients have been established, including highly specialized surgical techniques and multidisciplinary treatment programs.
A further area of expertise covers local recurrences of rectal cancer and rare ano-rectal tumors, such as melanoma and squamous cell carcinoma.

Special attention is paid to patients affected by gastrointestinal hereditary tumors, who are treated and followed-up by a dedicated team in collaboration with the Hereditary Digestive Tract Tumor Unit.

Since 2012, the Peritoneal Surface Malignancy (PSM) Program was included into the Colorectal Unit. This Program is focused on the treatment of pseudomyxoma peritonei, peritoneal mesothelioma, and peritoneal metastases from colorectal cancer.

KEYWORDS

Colorectal tumors
Gastrointestinal hereditary tumors
Pseudomixoma peritonei

BREAST SURGERY

HEAD OF UNIT

Secondo Folli

CLINICAL AND RESEARCH ACTIVITY

Four fields of interest have been developed during the considered biennium:

- Personalized axillary lymph node management in different subset of patients.
  a) Sentinel lymph node biopsy is always mandatory?
  b) Axillary dissection is always necessary in case of positive sentinel node?
  c) Is it possible to reduce the risk of breast cancer related lymphedema after axillary dissection by means of axillary reverse mapping and selective axillary dissection?
  Three randomized clinical trials have been activated to give an answer at these three unresolved questions.
- Treatment de-escalation for ductal carcinoma in situ of the breast with favorable prognosis;
- Oncoplastic approach in surgical treatment of breast cancer and innovative techniques for breast reconstruction;
- Supportive, integrative, complementary therapies.
  These activities explore alternative medicine, diet-food behavior and acupuncture to contrast side effects from adjuvant treatments in pre-menopausal women.

HIGHLIGHTS

SOUND, SINODAR and SAD trials are ongoing studies to investigate the more appropriate axillary management for staging and/or therapeutic purposes. Clinical data on outcome by using sentinel lymph node biopsy after neo-adjuvant chemotherapy have been published. *(Martelli G, et al. Eur J Surg Oncol. 2017 Nov;43(11):2012-2020).*

Treatment de-escalation and for active surveillance as intervention measure in selected patients with pre-invasive lesions. *(Gennaro M, et al. Breast. 2017 Oct;35:63-68).*

KEYWORDS

Treatment de-escalation
Active surveillance
Oncoplastic surgery
Integrative medicine

PLASTIC SURGERY

HEAD OF UNIT

Umberto Cortinovis

CLINICAL AND RESEARCH ACTIVITY

Clinical activity is mainly focused on breast reconstrution including lipofilling, prostheses, microsurgical and pedicle flaps.

Moreover, we collaborate with head and neck surgeons, sarcoma and thoracic surgeons, gynecologist and urologist and melanoma surgeons when a reconstruction is needed.

HIGHLIGHTS

Innovation project. The Unit is attually involved in a clinical study against capsular contracture with breast prostheses and radioterapy.

The target of the study is to evaluate if the use of Peak Plasma Blade in irradiated Baker III/IV capsular contracture patients who undergo expander or implant replacement with a new implant is related to an improvement of cosmetic-reconstructive outcomes and to a decrease number of complications, as shown in previous studies on healthy tissue.

KEYWORDS

Breast reconstruction
Prostheses
Skin cancer treatment
Soft tissue reconstruction
Lipofilling
Oncoplastic surgery

MELANOMA AND SARCOMA

HEAD OF UNIT

Mario Santinami

CLINICAL AND RESEARCH ACTIVITY

MELANOMA

Melanoma Surgical Unit is involved in all aspects of melanoma treatment.
The clinical staff provides visits for skin cancer diagnoses, surgical treatments in ordinary inpatient, day hospital and outpatient regimens, clinical follow-up and multidisciplinary care of patients with intermediate-advanced disease.
The Unit conducts trials on adjuvant therapy for stage III melanoma and is referring center for melanoma guidelines.
In December 2017 an Ocular Oncology Unit started its activity, focused on treatment of ocular melanoma and retinoblastoma.

SARCOMA

- Assessing the impact of neoadjuvant chemotherapy in localized high risk soft tissue sarcoma of the extremities
- Assessing the impact of neoadjuvant radiotherapy in localized primary retroperitoneal sarcoma
- Exploring non operative management of desmoid tumors
- Assessing the impact of definitive adron therapy as an alternative to surgery in sacral chordoma
- Exploring innovative prognostic models, integrating clinical, molecular and radiological information
- Molecular characterization of desmoid tumor, well differentiated/dedifferentiated liposarcoma, leiomiosarcoma and other rare histology subtypes.
- Characterizing the immunocontexture and immunomodulation in desmoid tumors
- Developing sarcoma subtypes cell lines as well as patients derived xenografts
- Coordinating the European School of Soft Tissue Sarcoma Surgery
- Coordinating the development of international guidelines for the management of Desmoid Tumors, Chordoma & Retroperitoneal Sarcoma

HIGHLIGHTS

MELANOMA

In 2017 the Melanoma Surgical Unit participated, as members of the International Melanoma Database and Discovery Platform, to the building of the new 8th AJCCmelanoma staging edition with an effort of more than 6,000 melanoma cases.

MELANOMA AND SARCOMA

Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. Gershenwald JE; Scolyer RA; Hess KR; Sondak VS; Long GV; Ross MI; Lazar AJ MD;Faries MB; Kirkwood JM; McArthur GA; Haydu LE; Eggermont MMA; Flaherty KT; Balch CM; Thompson JF.

The Melanoma Surgical Unit also participated to a study focused on melanoma patients survival after surgical and adjuvant treatment.
Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma.Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, Larkin J, Nyakas M, Dutriaux C, Haydon A, Robert C, Mortier L, Schachter J, Schadendorf D, Lesimple T, Plummer R, Ji R, Zhang P, Mookerjee B, Legos J, Kefford R, Dummer R, Ki JMN N Engl J Med. 2017 Nov 9;377(19):1813-182

SARCOMA

Development and validation of a nomogram to predict the risk of distant metastases and death of extremity soft tissue sarcoma *(Lancet Oncol 2016;17:671-680)* and development of an app (Sarculator) for friendly use in the clinic and research

Demonstration of the efficacy of neoadjuvant chemotherapy in high risk extremity soft tissue sarcoma in a large randomized study *(Lancet Oncol 2017;18:812-822)*

KEYWORDS

Melanoma
Surgery
Adjuvant treatments
Sarcoma
Desmoid Tumor
Chordoma
GIST
Prognostic factors
Survival

DIAGNOSTIC AND THERAPEUTIC ENDOSCOPY

HEAD OF UNIT

Enzo Masci

CLINICAL AND RESEARCH ACTIVITY

The activity has been focused on recent advances in diagnostic and interventional endoscopy in Oncology.
Great attention has been paid to high definition techniques such as endomicroscopy, digital chromoendoscopy and full spectrum endoscopy enabling physicians to recognize early dysplastic changes. Our efforts to recognize and treat early neoplastic lesions led us to focus on full thickness endoscopic resection techniques allowing endoscopists also to treat subepithelial lesions. Looking behind the wall, we kept our focus on Endoscopic Ultrasound guided procedures; by combining both trans-esophageal and trans-bronchial approaches, we are now able to guarantee a full, mini-invasive, inspection of the mediastinal space. Finally, in the field of bilio-pancreatic oncology we focused on the connection of Endoscopic Ultrasound with Endoscopic Retrograde CholangioPancreatography, which is essential to reach the best local staging and the less invasive interventional approach.

HIGHLIGHTS

Innovative and mini-invasive endoscopic procedures.
We implemented a mini-invasive diagnostic approach to the mediastinum, as described in the editorial published on GIED in December 2017 "Endosonography in the diagnosis and staging of mediastinal disease". The Unit reported innovative endoscopic procedures such as "EUS-guided fine needle aspiration of splenic vein thrombosis: a novel approach to the portal venous system" and "EUS-guided esophagoenterostomy for a completely obstructed surgical anastomosis" both published on Endoscopy in 2016.

New diagnostic tools.
We took part in a multicenter trial on Laser Endomicroscopy of Pancreatic asymptomatic cysts aimed to assess safety and diagnostic accuracy of a confocal probe inserted into the pancreatic cyst through a needle during EUS. We co-authored two papers, published on Tumori and Journal of Gastrointestin Liver Dis in January 2016 and June 2017, both focused on the role of capsule endoscopy in the setting of two rare GI diseases.

KEYWORDS

Therapeutic endoscopy
Endoscopic diagnosis
GastroIntestinal oncology

PEDIATRIC SURGERY

HEAD OF UNIT

Luigi Piva

CLINICAL AND RESEARCH ACTIVITY

This Unit was created in 2005 and collaborates with pediatric oncologists to provides a high standard of treatment for the most frequent solid, non central nervous system, tumors in children and adolescents. Clinical and reseacrh activities are focused on: renal tumors, germ cell tumors, rhabdomyosarcoma, lung surgical procedures, prophylactic colectomy for familial adenomatous polyposis.

HIGHLIGHTS

HRNBL1/SIOPEN:
for high-risk neuroblastoma, surgery is difficult, time consuming and its role is one of the primary objectives of the ongoing European Protocol, coordinated in Italy by our Institute.

AIEOP TCGM 2004 Protocol:
primary surgical excision represent the indication for all patients with localized disease of pediatric patients with teratomas and malignant germ cell tumors.

KEYWORDS

Pediatric surgery
Solid tumors

OTORHINOLARYNGOLOGY, MAXILLOFACIAL AND THYROID SURGERY

HEAD OF UNIT

Cesare Piazza

CLINICAL AND RESEARCH ACTIVITY

Our clinical and research activities have been focused in minimally-invasive transoral carbon dioxide laser-assisted surgery for early-intermediate laryngeal cancers; early detection of persistence/recurrence of previously managed tumors of the upper aero-digestive tract by Narrow Band Imaging; intraoperative neuromonitoring of recurrential nerves function during thyroidectomy and parathyroidectomy; free flaps reconstruction of various head and neck post-oncological primary and secondary defects; vertebral cervical somatectomy for bony tumors and metastases (in association with ortopaedics and neurosurgeons).

HIGHLIGHTS

Narrow Band Imaging (NBI) has been used with excellent results in detecting the presence and location of unknown primary squamous cell carcinoma of the upper aero-digestive tract, as described in Filauro et al. "Role of Narrow Band Imaging in detection of head and neck unknown primary squamous cell carcinoma" Laryngoscope 2018 Feb 2.

Conservative surgery for synovial sarcomas of the upper aero-digestive tract can be efficiently combined with pre- and/or postoperative (chemo)radiation in order to improve organ (larynx) and function (swallowing, voice and patent airway) preservation, still maintaining overall survival comparable to those reported in the literature for non-conservative surgical approaches, as reported in Paderno et al. "Synovial sarcomas of the upper aero-digestive tract: Is there a role for conservative surgery?" *Curr Opin Otolaryngol Head Neck Surg 2018; 26(2):94-101.*

KEYWORDS

Laryngeal laser surgery
Free flaps
Narrow Band Imaging
Head and neck sarcomas

GYNECOLOGIC ONCOLOGY

HEAD OF UNIT

Francesco Raspagliesi

CLINICAL AND RESEARCH ACTIVITY

Gynecologic oncology and research have made impressive progress in the last decades, based on understanding of key pathological events such as genetic and pathological features of various gynecological malignacies.
Our group coollaborated with other for the development of new therapeutic interventions also partecipating in large controlled clinical trials.
Studies span from basic research on receptors, signalling pathways and gene regulation, to the development of new surgical techniques aimed to improvbe patients' outcomes.

HIGHLIGHTS

Primary cytoreduction for patients with advanced/metastatic ovarian cancer

Our group published one of the larger experiences related to the implementation of extensive cytoreduction in ovarian cancer patients, thus supportting the quality of surgical care influes directely patients outcomes. To date, we are partecipating into a multicenter trial on the role of surgery in ovarian cancer patients.

Sentinel node mapping in endometrial cancer

Our group investigated the role of sentinel node mapping in patients affected by uterine cancer. Using sentinel node mapping, we imprive the detection of node positive patients,m reducing complications related to standard lymph node dissection, thus improving patients' quality of life. To date, we are conducing a prospective randomized trial to assess the best injection site for sentinel node mapping.

KEYWORDS

Ovarian cancer
Endometrial cancer
Cervical cancer

THORACIC SURGERY

HEAD OF UNIT

Ugo Pastorino

CLINICAL AND RESEARCH ACTIVITY

Thoracic Surgery Unit is characterized by minimally invasive surgery, complex reconstructive procedures, multidisciplinary approach to optimal treatment selection, comprehensive research on lung cancer biology and early detection, and continuous medical education.
Clinical activity is focused on pulmonary, mediastinal, chest wall and esophageal tumors, as well as lung metastases. Lung cancers is usually treated by 3D VATS lobectomy or segmentectomy, with neoadjuvant chemotherapy and broncho/angioplasty for advanced tumors, and selective lung-sparing procedures for curative lung metastasectomy.
Innovative reconstructive techniques have been developed, such as superior vena cava and major thoracic vessels replacement, and rib-like chest wall reconstruction of the entire hemithorax and diaphragm. Pleurectomy/decortication is proposed for limited malignant mesothelioma, after induction chemotherapy. Esophageal surgery is also performed with a 3D VATS approach.

HIGHLIGHTS

Tridimensional (3D) flexible VATS for minimal-invasive lobectomy, segmentectomy or esophagentomy in primary lung and esophageal cancer
In the last three years, the majority of patients have been treated with this technique, that combines the advantages of robotic surgery (tri-dimensional view, magnification and rotation) with lesser incisions and shorter operation time.

bioMILD trial
a prospective study testing the efficacy of plasma microRNA profiling plus low-dose computed tomography (spiral CT) as first line screening examination for earlier lung cancer detection and assessment of individual biologic risk. The 3-year follow-up of 4119 enrolled subjects will be completed by December 2018.

KEYWORDS

Minimal invasive lobectomy
Lung cancer screening
Precision surgery

UROLOGIC SURGERY

HEAD OF UNIT

Roberto Salvioni

CLINICAL AND RESEARCH ACTIVITY

Our main research activities are based on urothelial carcinoma. We have developed several clinical trials in different settings: neoadjuvant, adjuvant and metastatic.
In advanced/metastatic disease there is no standard of treatment, nor new drugs of proven efficacy so we have promoted several studies with molecular target therapies and immunocheckpoint inhibitors.
New clinical results have been very encouraging because of personalization of treatments in urothelial carcinoma and the identification of predictive and prognostic biomarkers of tumor response to immunocheckpoint inhibitors and targeted therapies.
Throught profit and no profit clinical trials we aim to deepen our knowledge of molecular mechanism of innate and acquired resistance and the relationship between tumor and microenviroment.

HIGHLIGHTS

PURE-01

An open label, single-arm, phase 2 study of neoadjuvant pembrolizumab (MK-3475) before cystectomy for patients with muscle-invasive urothelial bladder cancer.
The purpose of this study, in the recruitment phase, is to evaluate activity and efficacy of anti-PD-1 monoclonal antibody, at an early stage of treatment in patients with muscle-invasive urothelial bladder cancer.

PEANUT

An open label, single-arm, phase 2 study of pembrolizumab and nanoparticle albumin-bound paclitaxel in patients with metastatic urothelial carcinoma after chemotherapy failure.
The primary objective is to evaluate whether the combination of pembrolizumab and nab-paclitaxel is active and results in an increased activity compared to the available results with the use of both single-agents.

KEYWORDS

Surgery
Targeted therapy
Immunotherapy
Next Generation Sequencing

PLASTIC SURGERY LASER THERAPY

HEAD OF UNIT

Anna Colombetti

CLINICAL AND RESEARCH ACTIVITY

The Unit is dedicated to diseases where laser therapy is the first or only treatment and features high quality instrumentation including five lasers for a total of 26 wavelengths.
This allows both conservative and ablative therapies. Selective photothermolysis laser treatment is performed for keloids, pigmented and vascular lesions,while the laser ablation technique is used for mucosal and skin cancer lesions requiring histological evaluation. The lesions treated included: tumors: skin carcinomas, melanoma in-transit metastases, precancerous lesions such as actinic keratosis; vascular lesions: flat-type congenital capillary angiodysplasia, angiomas and venous lymphatic angiodysplasia;nevi:giant melanocytic nevi; hypertrophic scars and keloids; cutaneous localizations originating from complex syndromes, such as adenomas in tuberous sclerosis, angiodysplasias related to Sturge-Weber syndrome,neurofibroma and cafe-au-lait spots.
During 2017, 2,000 patients were treated at the Laser Unit.

HIGHLIGHTS

Neurofibromatosis type 1
the INT is a national referral center for laser therapy of cutaneous neurofibromas.

Skin carcinomas
The Unit deals with fragile patients suffering from systemic diseases: diabetes, organ transplantation, heart and vascular disease, cognitive deficits.The laser does not interfere with the electrical activity of pacemakers and defibrillators and can be used in patients with these devices.The haemostatic power of the laser beam allows the treatment of patients on anticoagulant therapy.

KEYWORDS

Laser therapy
Skin cancer
Angiodysplasia

DAY SURGERY

HEAD OF UNIT

Aldo E. Bono

CLINICAL AND RESEARCH ACTIVITY

The clinical activity covers many aspects of oncologic surgery. In particular, the surgical activity deals with different lesions involving skin, soft tissues, breast, as well lesions in gynaecologic, urologic, and head and neck areas.
This activity involves different surgeons of the Department of Surgery, sometimes working in cooperation. During the years 2016-2017, 15351 surgical procedures were performed. Of these interventions, 5694 were performed in a Day Hospital setting, whereas 9657 patients underwent outpatient surgery. 14551 operations were performed under local anesthesia, while 800 operations were performed under sedo-analgesia.
Clinical research activity is focused on melanoma. The aim is to better define the initial clinical features of early melanoma in order improve curative surgery.

HIGHLIGHTS

A new diagnostic system to detect early melanoma suitable for both patients and physicians has been developed called "CC" (Color-Change).
This approach covers the various aspects of melanoma that the traditional ABCD rule can miss out, particularly in case of small, nodular and amelanotic lesions (As easy as CC. Giornale Italiano di Dermatologia e Venereologia, 2016; 151: 211-2).

KEYWORDS

Day-Surgery
Early Melanoma

DEPARTMENT OF MEDICAL ONCOLOGY AND HEMATOLOGY

DEPARTMENTS AND UNITS

MEDICAL ONCOLOGY 1

Filippo de Braud

MEDICAL ONCOLOGY 2

Paolo G. Casali

MEDICAL ONCOLOGY 3: HEAD AND NECK

Lisa Licitra

MEDICAL DAY HOSPITAL

Roberto Buzzoni

HEMATOLOGY BONE MARROW TRANSPLANT

Paolo Corradini

PEDIATRICS

Maura Massimino

IMMUNOHEMATOLOGY AND TRANSFUSION MEDICINE SERVICE (SIMT)

Fernando Ravagnani

ONCOLOGY SUPPORTIVE CARE UNIT (SCU)

Carla Ida Ripamonti

MEDICAL GENETICS

Siranoush Manoukian

MEDICAL ONCOLOGY 1

HEAD OF UNIT

Filippo de Braud

CLINICAL AND RESEARCH ACTIVITY

The activity of the Division is focused to improve clinical care and outcomes of medical treatment of cancer through multidisciplinary management, personalized medicine and development of new drugs and therapeutic strategies.
For this aim, our Division includes Units fully dedicated to breast, gastrointestinal tract, genitourinary, lung cancer, melanoma and Phase I studies. The Unit is strictly connected to a preclinical laboratory focused on translational medicine to test novel therapeutic approaches.

Major areas of interest

New drug development (phase I and Ib studies); Identification of prognostic and/or predictive biomarkers to select patients to be treated with immune check point blockers and targeted therapy; role of high-dose chemotherapy in refractory/relapsed testicular cancer; evaluation of the metabolic effects on tumor growth and antitumor immunity of the fasting mimicking diet in cancer patients; multidisciplinary strategy to integrate chemio-radiotherapy and surgery.

HIGHLIGHTS

MET-driven resistance to dual epidermal grow factor receptor (EGFR) and BRAF blockade

MET amplification was identified as a new mechanism of resistance to EGFR receptor and BRAF dual/triple block combinations in BRAF-mutated colorectal cancer.
Prognostic and predictive role of Fumarate Hydratase in metastatic clear cell renal cell carcinoma.

Immunosuppressive mechanisms of triple negative breast cancer stem cells

The role of PDL1 (Programmed Death-Ligand 1) expresssion associated to cross-talk with SPARC (Secreted Protein Acidic and Rich in Cysteine) positive extracellular matrix. G48A, a New KRAS Mutation Found in Lung Adenocarcinoma.

KEYWORDS

New drugs
Clinical research
Translational research

MEDICAL ONCOLOGY 2

HEAD OF UNIT

Paolo G. Casali

CLINICAL AND RESEARCH ACTIVITY

Soft tissue and bone sarcomas

Disease characterization, translational correlations, medical therapy innovation, response and quality of life assesment, development of guidelines. Focus on very rare sarcoma subtypes.

Gastrointestinal stromal tumors (GIST)

Treatment innovations. Networking in rare cancers: organizational and methdological improvements in quality of care and research.

HIGHLIGHTS

Soft tissue and bone sarcomas

Publication of clinical studies and translational correlations (alveolar soft part sarcoma, clar cell sarcoma, chordoma, chondrosarcoma, desmoids, epithelioid sarcoma, giant cell tumor of bone, haemangioendothelioma, inflammatory myofibroblastic tumors, liposarcoma, solitary fibrous tumor, tenosynovial giant cell tumor).

GIST

Publication of results of major collaborative European/ international trials on adjuvant therapy and molecular targeted therapy in the advanced setting (long-term results).

KEYWORDS

Sarcoma
Rare cancers
Health networking

MEDICAL ONCOLOGY 3: HEAD AND NECK

HEAD OF UNIT

Lisa Licitra

CLINICAL AND RESEARCH ACTIVITY

Head and neck squamous cell cancer

Immunotherapy phase I - III trials participation; anti-EGFR (epidermal grow factor receptor) inhibitor afatinib trial; randomized phase II trial for tertiary prevention by nutritional intervention; identification of tumor and HPV-related infections by volatile organic compounds in breath; economic/health implications of 2 follow-up strategies after curative treatment; study for best management of chemo/radiotherapy-induced pain.

Development of a nasopharynx cancer international database

of clinical, epidemiological, translational data in non-endemic regions.

Paranasal sinus cancer

Sintart studies evaluating integrated treatment (chemotherapy+photon radiotherapy+adrotherapy+previous surgery).

Salivary gland cancer

2 Phase II trials with single kinase inhibitors, lenvatinib and axitinib; randomized EORTC (European Organization for Reseaarch and Treatment of Cancer) study on androgen deprivation.

Thyroid cancer

analysis of lenvatinib use in real-life

HIGHLIGHTS

Head and neck cancer

Anti-EGFR treatment refinement and predictive biomarker identification. B490 randomized trial proved that a 2-drug regimen (cetuximab-cisplatin) was noninferior in PFS (progressive free survival) while life-threatening toxicity was reduced. Multi-omics analysis of patients with extreme PFS difference enabled to identify that: Cluster3-subtype gene signature was strongly predictive of better outcome; Ras signature, overxpression of miRNA regulating EGFR signaling and hypoxia and presence of the CD274-PDCD1LG2 transcript fusion were associated to worst outcome. Validation of these potential predictors is ongoing in B490 trial samples. Combination of patient-specific (genomics, pathologic, clinic and imaging) and population-specific (epidemiologic, behavioral and environmental) data. An European project aimed to overcome the limits of the TNM staging system in risk stratification and treatment choice is ongoing. Innovative phase I and III immunotherapy studies are ongoing.

KEYWORDS

Targeted therapies
Head and neck squamous cell carcinoma
Nasopharyngeal carcinoma
Salivary gland carcinoma
Paranasal sinus carcinoma

MEDICAL DAY HOSPITAL

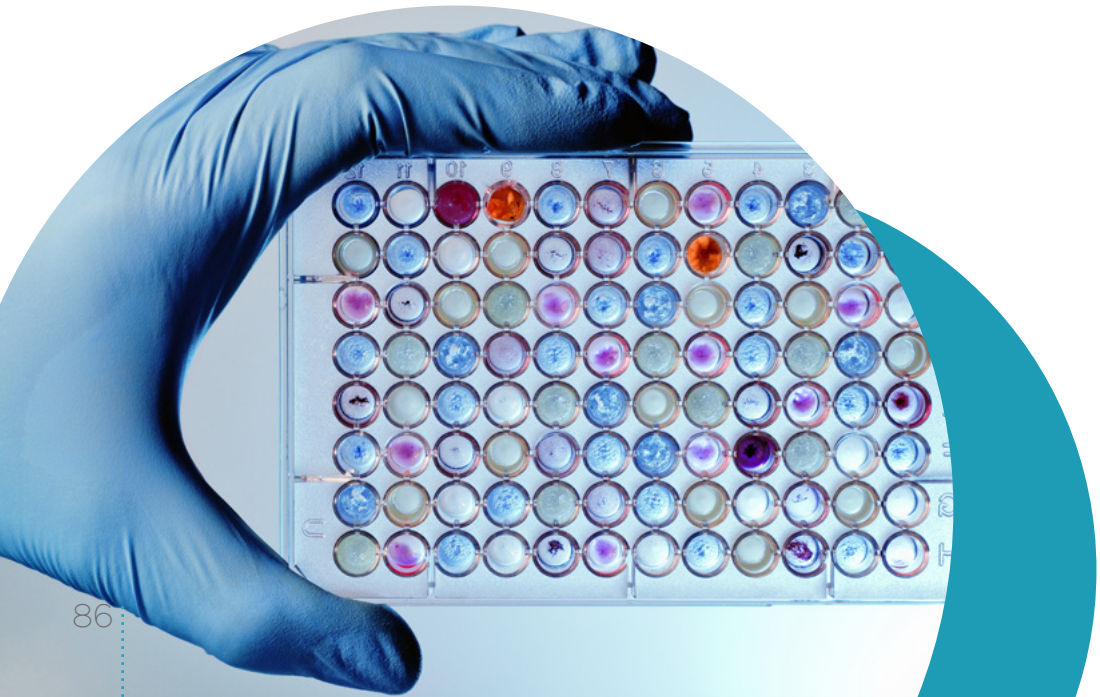
HEAD OF UNIT

Roberto Buzzoni

CLINICAL AND RESEARCH ACTIVITY

Our Unit features rooms for outpatient visits, waiting room, hospital rooms, oral medication dispensing rooms, and short infusional therapy rooms.

The oncological diseases treated are the following: breast cancer, gastrointestinal tumors, head/neck carcinomas, malignant melanoma, sarcomas, and neuroendocrine tumors.
About 300 patients are seen daily, and, of these, about 100 undergo medical treatment. Short duration therapies are performed in a large room with 11 dedicated chairs. Another room is dedicated to management of central line in order to minimize the risk of complications related to these devices. There are about 60-65 of these treatments per day.
There are 6 daily hospitalization rooms for a total of 18 beds and 5 chairs.
In addition, there is a room dedicated to mini-invasive treatments such as thoracentesis, paracentesis, lumbar puncture, bone marrow, and cutaneous biopsies. Research nurses are also involved in the collection of blood samples.
The Medical Day Hospital Unit is involved in several ongoing trials, sponsored and spontaneous.



HEMATOLOGY BONE MARROW TRANSPLANT

HEAD OF UNIT

Paolo Corradini

CLINICAL AND RESEARCH ACTIVITY

Hematology Unit is a leader in hematological malignancies care and research. It has a strong commitment to clinical and translational research on multiple myeloma (MM), indolent and aggressive non-Hodgkin's lymphoma (NHL), hematopoietic stem cell transplantation and immunotherapy.
The Unit controls a cell processing lab dedicated to preparing safe and effective hematologic cells for transplantation and a lab devoted to translational research to rapidly turn scientific discoveries into more effective and personalized treatment modalities.
The Unit, accredited from JACIE (European Joint Accreditation Committee), participates in national and international clinical research studies, providing patients access to new therapies including new combinations of drugs, CAR (chimeric antigen receptor)-T cells and monoclonal antibodies, new modalities for autologous or allogeneic stem cell transplantation, new treatments tailored to overcome aggressiveness and refractoriness driving lesions.

HIGHLIGHTS

Exploiting the role of potential genes/proteins as diagnostic tools and novel biomarkers for the early recognition/stratification of patients requiring intensified treatment options or those unlikely to respond to standard chemo-immunotherapies. The discovery of biological and/or molecular biomarker(s) of aggressiveness or chemo-refractoriness will lead to the development of innovative clinical programs with substantial impact in clinical practice.

New molecular method to detect minimal residual disease (MRD) in B cell malignancies. We are now applying a new next generation sequencing technology strategy based on the use of Ion Torrent Personal Genome Machine (PGM, Life Technologies) to monitor MRD in B cell malignancies and clonal evolution in MM patients. We have also introduced and developed molecular tests for the detection of mutation with diagnostic impact in hairy cell leukemia, Waldenstrom macroglobulinemia, peripheral T cell lymphomas and myeloproliferative disorders.

KEYWORDS

Lymphoma
Allogeneic transplantation
Myeloma

PEDIATRICS

HEAD OF UNIT

Maura Massimino

CLINICAL AND RESEARCH ACTIVITY

Unit activity is based on the treatment and study of solid tumors of infancy, adolescence, and young adulthood with the largest accrual of solid tumors in Italy.
During 2016 and 2017, over 250 new patients/year were diagnosed and treated. In 2017 an ocular oncological unit was also implemented for retinoblastoma treatment, ocular pathway glioma evaluation and ophtalmologic event care. Activities are managed in both inpatient and outpatient regimens, involving social support, education, sport continuation, cured patient follow-up, fertility preservation programs, and throughout psychological support for children, adolescent and families. A palliative care program is also in place. Around 100 surgical and over 150 radiation treatments/year were performed for malignant tumors. A total of 52 autologous bone-marrow transplantations were performed for high-risk/relapsed solid tumors. Over 75% patients were treated within clinical controlled trials also including phase 1 and 2 with new drugs

HIGHLIGHTS

Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma *(Massimino M. et al, Neuro Oncol. 2016;18:1451-60)*
In a national multi-institutional collaboration, with the largest sample of ependymoma patients in a prospective trial to date, feasibility of multiple surgical procedures followed by a novel radiotherapeutic approach that have been used as the basis for the European prospective protocol for childhood ependymoma.

A total of 3 phase 1 and 2 trials, 8 academic interventional trials and 4 observational trials have been opened to accrual.

KEYWORDS

Childhood tumors
Adolescents
New drugs
Follow-up
Sequelae

IMMUNOHEMATOLOGY AND TRANSFUSION MEDICINE SERVICE (SIMT)

MEDICAL ONCOLOGY AND HEMATOLOGY

HEAD OF UNIT

Fernando Ravagnani

CLINICAL AND RESEARCH ACTIVITY

SIMT provides clinical services to support patients in need of blood components (also for Istituto Neurologico Besta), cellular therapy and therapeutic apheresis.
The Unit is involved in handling all aspects of donor recruitment for whole blood products, apheresis products, and the auto-transfusion program collects.
During 2016-17, the Unit determined eligibility on 1,076 potential blood donors collecting 15,430 donations, and evaluated elegibility of 350 putative bone marrow donors.
The Apheresis Collection Facility is responsible for peripheral blood autologous and allogeneic hematopoietic stem cells collection and for therapeutic aphereses, mainly extracorporeal photopheresis and plasma exchange (997 procedures).
The Unit includes specialized laboratories:

- Immunohematology
- HLA Laboratory; from March 2017 "Chimerism Analysis" was introduced in patients who have undergone allogeneic stem cell transplant.
- Serology and molecular virology; in June 2016 EBV-DNA assay was set up.

HIGHLIGHTS

Validation of circulating EBV-DNA as tumor biomarker in nasopharyngeal cancer (NPC) patients in non-endemic areas.
In collaboration with Head and Neck Medical Oncology Unit of our Institute, we are evaluating the prognostic value of EBV DNA load in EBV-related NPC patients, as assessed in endemic areas. The role of pre-treatment plasma EBV-DNA in 130 locally-advanced NPC patients has been published (*Alfieri S. et al, Oncotarget 2017*).

Adoption of Patient Blood Management (PBM)
PBM is a fundamental program in order to diminish risk, improve outcomes and reduce costs associated with excessice blood utilization.
Adoption of PBM started with multidisciplinary meetings to define a strategy and encouraging single-unit red blood cell transfusion in stable patient

KEYWORDS

Transfusion Medicine
HLA and chimerism
Virology
Apheresis

ONCOLOGY
SUPPORTIVE CARE UNIT (SCU)

HEAD OF UNIT

MEDICAL ONCOLOGY AND HEMATOLOGY

Carla Ida Ripamonti

CLINICAL AND RESEARCH ACTIVITY

SCU provides planned/unplanned interventions to manage medical complications of outpatients suffering from metabolic alterations, dehydration, infections, anemia, comorbidities and all oncologic treatment related toxicities according to ESMO, MASCC, WHO international guidelines.

2016-17 clinical activity

9,617 visits, 6,675 drug infusions or hydration, 1,561 bisphosphonates/denosumab, 1,919 transfusions, 2,172 treatments in DayHospital/MAC.

Areas of excellence

- All patients are assessed for the presence and intensity of physical and emotional symptoms, spiritual and social concerns; hope, dignity and comunication needs by means of assessment tools validated in the SCU;
- multispecialistic team with multidisciplinary clinical approach that improve the quality of care and decrease the number of hospitalizations;
- geriatric assessment for patients before surgery/trials;
- geriatric supportive care;
- direct access for urgent unplanned complications;
- virtually no waiting list.

HIGHLIGHTS

Among the SCU areas of research we underline the following:

SCU save resources for Health Care System (HCS): a dedicated SCU aimed at monitoring and treating cancer therapy-related toxicities and comorbidities reduce n. of hospitalizations and provides an economical benefit for HCS when blood transfusions are performed in SCU in respect to Hospital wards *(Ripamonti et al. Tumori 2017)*

Weak opioids: is the WHO 2nd step necessary to treat pain in cancer patients? In patients with cancer and moderate pain, low-dose morphine reduce pain intensity significantly compared with weak opioids with earlier effect and tolerability *(Bandieri et al. JCO 2016)*

Hope and spirituality in non-advanced cancer patients: Hope can be encouraged by clinicians through dialogue, sincerity, and reassurance, conisdering patients' needs, symptoms, distress and their spiritual/religious resources *(Ripamonti et al. Annals of Oncology 2016)*

KEYWORDS

Treatment-related toxicity
Supportive care
Continuity of care
Quality of life
Out-patients
Elderly cancer patients

MEDICAL GENETICS

HEAD OF UNIT

Siranoush Manoukian

CLINICAL AND RESEARCH ACTIVITY

The Unit provides genetic counseling for hereditary cancer syndromes and the diagnostic activity is integrated with several research programs.

Main focus is Hereditary Breast and Ovarian Cancer syndrome (HBOC), other rare inherited predispositions to cancer are also investigated. During 2016-17, about 1,600 new families asked for a risk evaluation. To rationalize access to genetic counseling/testing, a first clinical evaluation was performed and only eligible patients fulfilling INT selection criteria underwent genetic counseling/testing.

Consolidated activity allowed the collection of the largest Italian cohort of HBOC families (>4,970, including >11,030 individuals):

- all relevant data recorded in the dedicated database (>970 families with BRCA (BReast CAncer gene)1/2 pathogenic mutations and >190 families with unknown genetic variants);
- tumour specimens and blood samples collected from all patients treated at INT;
- clinical, familial, pathological and molecular data updated.

HIGHLIGHTS

Clinical/Molecular characterization of HBOC

Collected data and biological specimens, of a selected population has allowed research studies conducted with other INT Units, national/international collaborations and partecipation to consortia, on:

- biological and clinical significance of BRCA gene mutations with unknown significance genomic analyses for the identification of modifier risk factors and new genes involved in genetic predisposition to HBOC;
- effective strategies for identification and referral to risk evaluation of women at increased -genetic risk for breast and ovarian cancer;
- Breast Cancer Association Consortium (BCAC);
- The Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA);
- Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA);
- Hereditary Breast Cancer Clinical Study Group;
- The IMPACT study (Identification of Men with a genetic predisposition to ProstAte Cancer);
- DIVA Project (Database Italiano VArianti geni BRCA1/2).

KEYWORDS

Hereditary Breast/Ovarian cancer
Genetic predisposition
Genetic counseling/testing
Risk assessment

DEPARTMENT OF DIAGNOSTIC IMAGING AND RADIOTHERAPY

DEPARTMENTS AND UNITS

RADIATION ONCOLOGY 1

Riccardo Valdagni

RADIATION ONCOLOGY 2

Carlo Fallai

DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY

Alfonso Marchianò

NUCLEAR MEDICINE

Flavio Crippa
Ettore Seregni

MEDICAL PHYSICS

Emanuele Pignoli

RADIATION ONCOLOGY 1

HEAD OF UNIT

Riccardo Valdagni

CLINICAL AND RESEARCH ACTIVITY

Radiation Oncology 1 (RTO1) provides radical and palliative radiation (RT) to patients with a multidisciplinary approach and according to national and international guidelines or research protocols.
In 2016 and 2017, 1469 and 1861 patients were treated, respectively.
Particular attention and efforts are dedicated to improve new technologies, such as VMAT and IGRT (Calypso). Hypofractionation is routinely used. RTO1 partecipates in international trials and focuses its research activity on the following areas: the development of predictive models of radioinduced toxicity with evaluation of clinical, radiomics and genetic variables and the validation of that at an international level, especially in prostate cancer. Another research area regards comparison of toxicity data and predictive modeling in European multicenter project (REQUITE) in breast, lung and prostate cancer; RT techniques and fractionations, such as hypofractionated and partial breast irradiation.

HIGHLIGHTS

Retrospective and prospective study of late radiation damages after focal radiotherapy for childhood brain tumors.

To correlate radiotherapy dose levels to different areas or structures of the brain with neurocognitive damage and behaviour problems in pediatric patients surviving brain tumors. As a results, RT treatment planning techniques could be significantly optimized to spare more sensitive brain areas thus reducing the iatrogenic neurocognitive morbidity and improving quality of life in these children.

EORTC STRASS Trial

A phase III multicentric randomized study to compare surgery alone vs preoperative radiation therapy + surgery in retroperitoneal sarcoma. It started on 2012 and closed on 2017 for completed recruitment. The primary endpoint is local control. We are waiting for final results. An interim analysis showed a good compliance for both arms and demonstrated that radiotherapy is a safe approach without increasing a perioperative morbidity.

KEYWORDS

Personalized radiotherapy
Predictive models of radio-induced toxicity
IGRT
Hypofractionated radiotherapy
New technologies
Multidisciplinarity
Quality of life

RADIATION ONCOLOGY 2

HEAD OF UNIT

Carlo Fallai

CLINICAL AND RESEARCH ACTIVITY

Inpatients activity

Radiation Oncology 2 has a section with eight beds for patients needing hospitalization for radiotherapy or radio-chemotherapy procedures, supportive therapy, and interventional manoeuvres. During 2016 and 2017, there were 608 hospitalizations.

Outpatients activity

Radiotherapy of Head and Neck Cancer is an essential part of the activities of the Head and Neck Cancer Multidisciplinary Group. In 2016-7, 385 patients affected with head and neck cancer were irradiated. All patients treated with curative intent were treated with VMAT.
The radiation treatment of gynecologic cancers is also an essential part of our activities. During 2016-7, 246 patients were treated with external beam radiotherapy (VMAT) and/or High-Dose Ratebrachytherapy (HDRBCT). One hundred and twenty-five patients had brachytherapy as part of their treatment with 450 procedures.
Overall, mostly in the cervix cancer, 338 cycles of concurrent chemotherapy were given.

HIGHLIGHTS

Head and neck cancer. SINTART 1 – 2

Multidisciplinary approach for bad prognosis sinonasal tumors: a phase II study about integration of surgery, chemotherapy, radiotherapy with photons and/or heavy ions looking for more efficient and less toxic treatment both in operable or inoperable patients (approved 27/4/2015, del. n. 230/F session n. 43).
For heavy ions, a cooperation was agreed on with the CNAO center in Pavia. To date, 26 patients were enrolled in SINTART-2 TRIAL (ongoing), 31 patients in SINTART-1 study (ongoing).

Ginecologic cancer. Gynadart

"Adaptive" and MRI guided Brachytherapy in the exclusive treatment of locally advanced cervix cancer according to the European excellence standards: study of the treatment quality in terms of applicability, clinical and dosimetric outcomes.(INT 53/15) GD Del. 28/08/2015. Forty patients with locally advanced cervix cancer (FIGO IB2-IVA) underwent brachytherapy, with MRI used for treatment planning before each session (trial closed).

KEYWORDS

Head and neck cancer
Gynecologic cancer
Brachytherapy
Brain radiosurgery

DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY

DIAGNOSTIC IMAGING AND RADIOTHERAPY

HEAD OF UNIT

Alfonso Marchianò

CLINICAL AND RESEARCH ACTIVITY

Diagnostic oncology and interventional-oriented radiology represent the core activity of the Unit.
Inpatients and outpatients undergo a diagnostic work-up that includes different steps of patient management: primary cancer diagnosis, staging, follow-up, and monitoring after surgery, chemotherapy, and radiotherapy. Images are managed by a centralized system, locally accessible by the various professional figures on the basis of their clinical and research needs.
The update of the technological equipment of the department went on in 2016-2017.
In particular, INT was equipped with a new angiography facility representing the state of the art in this field of crucial importance for oncological interventional procedures.
Moreover an additional Magnetic Resonance scanner (1.5 Tesla) and the most recent prone stereotactic system for breast biopsy with 2D and 3D imaging were installed.
The system provides superior imaging and gives 360-degree access to the breast.

HIGHLIGHTS

The main clinical research activities involved:
lung cancer screening program (bioMILD) with low dose CT, treatment of hepatocarcinomas by intra-arterial radioembolization with Y-90 microspheres, optimization of drug-eluting bead chemoembolization techniques by new generation of small particles and radiomic analysis of soft tissues sarcomas and head and neck tumors.

KEYWORDS

Interventional radiology
Screening
Breast biopsy

NUCLEAR MEDICINE

HEAD OF UNIT

Flavio Crippa
Ettore Seregni

CLINICAL AND RESEARCH ACTIVITY

Nucler Medicine Unit is a center of expertise for clinical research, diagnostic and therapeutic application in oncology,
with particular regard to targeted radionuclide therapy (treatment of neuroendocrine tumour, thyroid cancer, prostate cancer), hybrid imaging (PET-CT and SPECT-CT), radioguided surgery and development of new target therapy for neuroendocrine cancer.
The Unit is one of the few centers in Italy treating neuroendocrine tumors with Peptide Receptors Radionuclide Therapy (PRRT) and is one of the leading center for the treatment of liver tumors with dosimetric calculation of ^{90}Y microspheres. It is equipped with two PET/CT, one SPECT/CT and two gamma cameras, and is provided with two radiochemistry laboratories.

HIGHLIGHTS

The main research fields include:

Yttrium-90 transarterial radioembolization (TARE) of hepatocellular carcinoma with dosimetric calculation for the evaluation of safety and efficacy of a personalized approach.

Phase II study of tandem treatment with ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE of neuroendocrine tumors refractory to conventional therapies

KEYWORDS

PRRT
^{90}Y-TARE
PET-CT
Thyroid cancer
Neuroendocrine cancer

MEDICAL PHYSICS

HEAD OF UNIT

Emanuele Pignoli

CLINICAL AND RESEARCH ACTIVITY

Main areas of research:

- study on a 6 Degree of Freedom robotic couch to improve patient setup and radiotherapy reproducibility, in particular for patients with single or multiple brain metastases and head-neck tumours.
- study of the white and gray matter alterations visible with RM after focal radiotherapy for childhood brain cancer to correlate radiotherapy doses, neurocognitive outcome and behavioral problems. Preliminary data showed some of the potential brain areas where radiotherapy dose and cognitive tests results were significantly related and the corresponding preliminary threshold dose levels. A pilot study on repeatability and reproducibility of radiomics features extracted from CT and MR images in phantoms and their variation as function of the diagnostic protocols acquisition parameters. In collaboration with the CNAO implementation of new protocols for the application of hadron and photon beams radiotherapy for the treatment of head and neck, pediatric and prostate cancer.

HIGHLIGHTS

Radiomics

Investigation of the radiomic features arising from CT and MR images in order to identify indicators and predictors of cancer evolution or response to treatments, especially radiotherapy.

Brain alteration in childhood focal brain irradiation

Investigation of white and gray material alterations after childhood focal brain irradiation to assess correlations between dose levels in different brain areas and neurocognitive outcome.

MICRO-LEARNER

Investigation of MICRObiota, infLammatory Environment, clinicAl and Radiomic features as predictors of Normal tissue response in radiotherapy for prostatE and head-and-neck canceR

In vivo dosimetry in HDR brachytherapy

In collaboration with the Centre for Medical Radiation Physics of the University of Wollongong (Australia) a system for in vivo doismetry was designed and applied to patients treated for gynecological and prostate cancers with high dose rate brachytherapy.

KEYWORDS

Dosimetry
Radiomic features
Radiotherapy
Brachytherapy

DEPARTMENT OF DIAGNOSTIC PATHOLOGY AND LABORATORY MEDICINE

PATHOLOGY 1

Giancarlo Pruneri

PATHOLOGY 2

Giancarlo Pruneri

LABORATORY MEDICINE

Daniele Morelli

PATHOLOGY 1

DIAGNOSTIC PATHOLOGY AND LABORATORY MEDICINE

HEAD OF UNIT

Giancarlo Pruneri

CLINICAL AND RESEARCH ACTIVITY

The Division participated in clinico-pathological research involving institutional departments and national collaborative groups.
Its effort was particularly devoted in the analysis of putative prognostic/predictive biomarker of immunotherapy or chemosensitivity in breast cancer patients, and in the analysis of risk subroups in gastrointestinal neuroendocrine carcinoma, based on the assessement of tumor proliferative activity by means of the highly distributed and potentially reproducible method of immunohistochemical evaluation of Ki-67 antigen.

HIGHLIGHTS

Modulation of Immune System and Adjuvant Chemotherapy in Breast Cancer.
A prospective study on breast cancer patients treated with adjuvant therapy to identify the schedule and therapeutic phase mainly associated with immune system activation and, thus, immunogenic cell death. The main leukocyte subsets and the Teff/Treg lymphocyte ratio, known to affect tumor progression and prognosis, were evaluated by multicolour flow cytometry in the peripheral blood of 10 patients during 17 time-points of treatment.

The Clinicopathologic Heterogeneity of Grade 3 Gastro-enteropancreatic Neuroendocrine Neoplasms: Morphological Differentiationand Proliferation Identify Different Prognostic Categories.
Milione et al. euroendocrinology 2017;104(1):85-93.
The study suggests that GEP NECs represent a heterogeneous group of neoplasms which can be better classified in different prognostic categories using proliferative index.

KEYWORDS

Breast cancer
GE cancer
Microenvironment

PATHOLOGY 2

DIAGNOSTIC PATHOLOGY AND LABORATORY MEDICINE

HEAD OF UNIT

Giancarlo Pruneri

CLINICAL AND RESEARCH ACTIVITY

The activity has been highly translational, based on the analysis of putative predictive/prognostic biomarkers with updated technologies including: multicolor flow cytometry, fluorescent PCR and capillary electrophoresis for B- and T-cell clonality testing, chromogenic and silver in situ hybridization, Sanger sequencing and next-generation sequencing (NGS). The activities were developed within the context of institutional, national and international collaborative groups and networks.

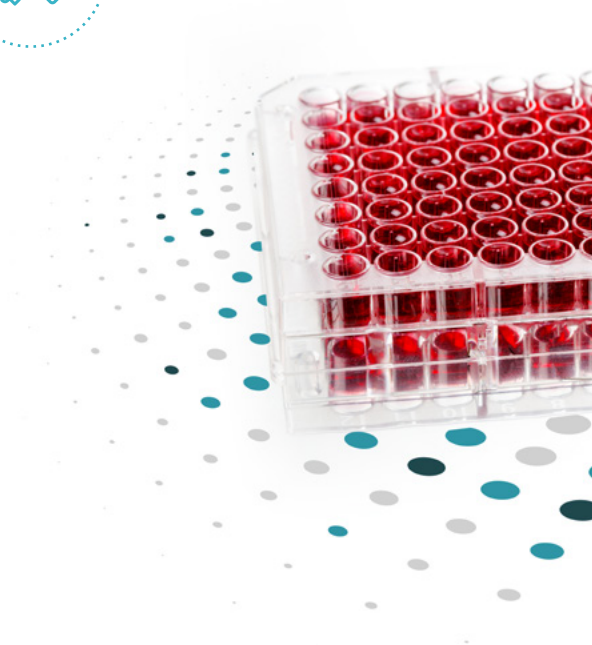
In particular, the Division was involved in the study of rare diseases, including soft tissue sarcomas and pediatric tumors, as well as peritoneal mesotheliomas, hematopoietic disorders and breast cancers.

HIGHLIGHTS

Evaluation of the prognostic relevance of miRNA expression in colorectal, breast and thyroid carcinoma and in melanoma.

KEYWORDS

Translational research
Rare tumors
Next Generation Sequencing



LABORATORY MEDICINE

HEAD OF UNIT

Daniele Morelli

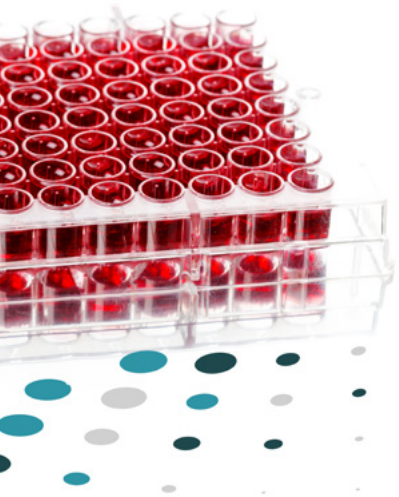
CLINICAL AND RESEARCH ACTIVITY

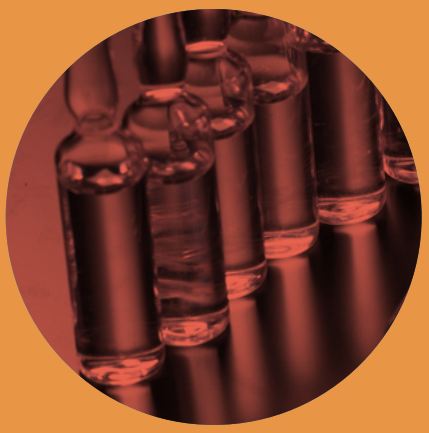
Laboratory Medicine performs biological tests and microbiological investigations that contribute to the diagnosis, prognosis, and monitoring of oncologic patients submitted to conventional and experimental therapies.

About 2,000,000/year examinations were performed. The reliability of the results is guaranteed by maintaining high quality standards, which are constantly monitored by national and international External Quality Assessment (EQA).
Much attention has been paid to the choice of appropriate technologies and to the continuous improvement of technical and scientific knowledge of the medical and scientific staff.
Moreover, the Unit tests new technologies and analytical methodologies and transfers scientific know-how relative to the clinical laboratory to professionals and students.
The Unit is also involved in evaluation of the diagnostic potential of new tests and technologies and in the search for innovative organizational solutions.
The Unit is engaged in support activity for several clinical trials conducted at the INT.

KEYWORDS

Clinical chemistry
Hematology
Microbiology





SCIENTIFIC REPORT 2016-2017

ADDITIONAL INFORMATION

ADDITIONAL INFORMATION

INT AND TECHNOLOGY

RESEARCH CORE FACILITIES

EDUCATION

SCHOLARLY OUTPUT

SELECTED PAPERS

Complete and detailed list of publications in appendix at http://bit.ly/2aYvFiB

CLINICAL RESEARCH ACTIVITY

Complete and detailed list of ongoing clinical studies in appendix at http://bit.ly/2aYvFiB

RESEARCH FUNDING

Complete and detailed list of ongoing funded projects in appendix at http://bit.ly/2aYvFiB

ETHICS COMMITTEE

INT AND TECHNOLOGY

AVAILABLE TECHNOLOGY FOR DIAGNOSTICS, THERAPY, SURGERY AND RESEARCH

In the field of diagnostics and therapy, INT stands out for its latest generation equipment which, in addition to their daily clinical use, is also used for research purposes. Favoured by an adequate hardware and software infrastructure, in INT diagnostic and therapy work in complete synergy, both in the clinical and research fields. In some specific cases, INT contributes in a research context also to the technological evolution and optimization of peculiar equipment, and to the implementation of new applications.

HIGHLIGHT
FUNCTIONAL GENOMICS AND MULECULAR ANALYSIS PLATFORMS

Technology innovation and next-generation sequencing (NGS) play a fundamental role in precision medicine whose final goal is providing the right treatment to the right patient in the right moment. INT is at the forefront for applying NGS technologies in diagnosis and translational research in order to identify novel biomarkers and therapeutic targets, as well as for patient stratification by mutational analysis. Thanks to last generation instrumentation, INT supports basic and translational research in the field of precision medicine, that can be applied to patients thanks to high technology instrumentations in diagnostic and therapeutic fields.

The Functional genomics platform for diagnostic and therapeutic optimization for precision medicine, available at the Functional Genomics Core Facilities, employs high performing instrumentations to perform nucleic acid extraction, purification and quality controls, automation and liquid handling workstations; microarrays platforms for gene, miRNA, lcnRNA expression (Ilumina); DNA methylation, CGH, SNP and copy number variation (GeneChip); Next generation sequencing (Ion Torrent, Ion 5SXL, NextSeq500). In 2016-17 new instrumentations have been acquired: the ION Ion 5SXL next-Generation DNA sequencer for massive sequencing; the Janus robotic station for liquid handling; the GeneChip System for expression and DNA analysis; a droplet digital PCR.

The DEP Array System combines the ability to manipulate individual cells using DEP technology with high quality image-based cell selection. It identifies and recovers specific intact and viable individual cells of interest from complex, heterogeneous samples, available for further analysis, including next generation analysis.

The Vectra 3 acquired in 2017 automated quantitative pathology imaging system performs immuno-profiling and phenotyping of multiple immune cell subsets in situ in Formalin-Fixed Paraffin-Embedded (FFPE) tissue sections (Phenoptics), to increase knowledge in prognostic and predicting value of immune contexture in neoplastic regions.

The Flow cytometry and cell sorting equipment has been improved in 2016-17 by upgrading and acquiring novel instruments.

HIGHLIGHT RADIATION ONCOLOGY

Radiation Oncology at INT follows the modern concept of "personalized treatment", thanks to the availability of equipment that meets the highest technological standards (VMAT delivery, integrated CBCT imaging devices, 6D couch, flattening filter free high dose rate beams). In particular, INT is one of the very few centres in Italy with an exclusive system to monitor the movement of the target region during treatment delivery. The system is based on the implantation of small electromagnetic transponders inside or very close to the tumour (currently implemented for the prostate). In 2016-17 INT was equipped with a new dedicated CT scanner which delivers images that are optimized for both organ contouring and dose calculation. Moreover, a new brachytherapy facility was installed, including a high speed workstation for dose calculation and a suite fully dedicated to prostate.

Available equipment:

- 6 linear accelerators
- 1 brachytherapy unit
- 2 dedicated CT scanners
- 9 workstations for treatment planning and dose calculation

HIGHLIGHT RADIOLOGY AND DIAGNOSTIC IMAGING

Radiology at INT is characterized by the high quality of the obtained diagnostic images, balanced by the continuous search for an optimization (reduction) of the dose of radiation delivered to the patient. Images are managed by a centralized system, locally accessible by the various professional figures on the basis of their clinical and research needs. In particular, INT was equipped in 2016-17 with a new angiography facility representing the state of the art in this field. The machine consists of a latest generation rotational angiography system, aimed at dose reduction and optimization of rotationally acquired images of crucial importance for oncological interventional procedures. Moreover, the most recent prone stereotactic system for breast biopsy with 2D and 3D imaging was installed. The system provides superior imaging and gives 360-degree access to the breast.

Available equipment:

- 6 Magnetic Resonance scanners (1.5 Tesla)
- 1 CT scanners
- 2 Tomosynthesis and mammographic scanners
- 9 prone stereotactic system for breast biopsy with 2D and 3D imaging.
- 2 angiographs
- 22 further radiological equipment

INT AND TECHNOLOGY

HIGHLIGHT NUCLEAR MEDICINE

Nuclear Medicine at INT meets the highest standards of functional imaging and metabolic therapy. In particular, with regard to imaging, INT was equipped in 2016-17 with a new PET/CT scanner provided with a system for the acquisition of images synchronized with the patient's respiratory movement. With regard to therapy, INT is one of the very few centres in Italy treating liver tumours with ^{90}Y microspheres provided with a treatment planning system for 3D dose distribution calculation.

Available equipment:

- 2 PET/CT scanners
- 1 SPECT/CT scanner
- 2 SPECT scanners
- 1 workstation for 3D calculation of the dose delivered with ^{90}Y microspheres

HIGHLIGHT ENDOSCOPY AND SURGERY

The operating rooms at INT are provided with a state of the art integration system designed to simplify and streamline the operating rooms by consolidating data, access to video, diagnostic images and controls for all the devices at a central command station. The system, which allows the surgical staff to perform many of their tasks efficiently, was updated in 2017.
In 2016-17 some surgical units at INT were provided with a new telemetry system that provides real-time patient's information and allows data to be collected remotely. Moreover, a broad band wide-angle endoscopy system is now available. The system allows highly accurate diagnostic gastroscopy and colonscopy, given the number and size of the viewing angles of the cameras placed in the distal end of the optic. This allows to improve the detection rate of colon polyps and duodenum and papilla lesions. Among the available surgical instruments, noteworthy is also the videolaparoscopy system for fluorescence imaging, which uses the green indocyanine tracer (non-radioactive) during surgery for neoplastic disease and sentinel lymph node mapping.

HIGHLIGHT PATHOLOGICAL ANATOMY

In the context of precision medicine as the foundation for personalized medicine, the new Next Generation Sequencing technology is used at INT not only for research aims, but also to support therapeutic decisions and diagnosis, if deemed appropriate by the clinician, especially for lung and colorectal cancer, and melanomas. Among dedicated equipment, Ion 5SXL and CE-IVD certified PGM (acquired in 2017) are used to detect variants by targeted gene sequencing and establish the specific mutational status of each tumor, by systematic use of a commercial gene panel of the 50 genes most commonly mutated in cancers, as well as mutational panels designed by INT researchers. The nCounter FLEX Analysis System, Nanostring, employs a novel digital barcode technology for direct multiplexed measurement of analytes, offering high levels of precision and sensitivity, allowing rapid biomarkers identification starting from low quantity biological material, integrating NGS approach for translational research.

HIGHLIGHT PHARMACY

The Pharmacy unit is provided with a state-of-the-art facility for centralized and automated chemotherapy preparations. In particular, the 5 clean rooms are equipped with 2 robots for compounding sterile preparations and with 5 workflow engine systems for the assisted preparation and computerized management of patients tailored treatments. Chemo medications are labelled with a QrCode and delivered to the wards by pneumatic mail.

RESEARCH CORE FACILITIES

GRANT OFFICE

The INT Grant Office provides timely advice and information to researchers on funding opportunities; coordinates the participation of the research projects to funding programs; provides information on the internal procedures for submissions of project proposals; supports researchers to the submission and the final financial report and audit processes.

FUNCTIONAL GENOMICS AND BIOINFORMATICS

The Functional Genomics And Bioinformatics (FGBCF) provides technological support to translational oncology through the development and implementation of advanced experimental methods with dedicated equipment and platforms. Genomics focus on the genetic information stored in DNA and aim at identifying the different activity of genes in distinct cell populations or in response to different treatments. Bioinformatics develops and applies computational methods for analyzing genetic sequences or gene expression data.

TECHNOLOGY TRANFER OFFICE

The INT Technology Transfer Office (TTO) was created in 2009 to address two requirements: improve research results in a scientific and economic key and optimize processes in technology transfer and intellectual property management. The TTO offers support services for patent activities (from the beginning of a new invention to the filing and maintenance of the correspondent patent), spin off evaluation and dissemination of Intellectual Property culture within researchers.

CLINICAL TRIALS CENTER

The Clinical Trials Center supports Clinical Researchers in many aspects of investigational clinical studies, such as study design, statistical analysis/validation, data management, submission to Ethics Committees/regulatory authorities, budget and contract related issues, pharmacovigilance by dedicated personnel including data managers, statisticians, research nurses and administrative personnel.
In the biennium, the CTC managed 365 clinical studies; 145 of which investigatordriven.

TISSUE AND CELL REPOSITORY

Departments of Pathology and DRAST have implemented and maintain a large bank of frozen and FFPE normal, tumor tissues and blood/plasma/serum samples, collected and stored within a short time from removal following SOPs. Thousands of well-annotated clinical specimens of different tumor histotypes, linked to dedicated databases of patho-biological and clinical information, are currently available. Patients sign an informed consent which allows INT investigators to use the left over material of biological samples collected during standard surgical and medical procedures for research purposes. Aliquots are attributed to individual studies after approval of Institutional Review Board and specific requests to the Ethical Committee. All left over material is stored in the Institutional BioBank for at least 20 years from the collection, including residual material of specific project studies.

BIOMEDICAL LIBRARY

The INT Library is affiliated to the European Association for Health Information and Libraries. It offers a large collection of basic science journals and reference books, and electronic access to the full text of scientific and clinical journals, databases and books.

LABORATORY ANIMAL FACILITY

Animal facilities authorized by the Italian Ministry of Health for housing transgenic and immmunodeficient mice under standard pathogen-free conditions and, when needed, in isolators vented with sterile HEPA-filtered air. Proteomics/ Mass Spectrometry Laboratories

OTHER FACILITIES

- Immunohistochemistry
- Cell imaging facility
- Flow cytometry and cell sorting
- Proteomics/Mass Spectrometry Laboratories

EDUCATION

As a comprehensive cancer centre for excellence, INT is deeply committed to quality education and training. Postdoctoral research fellowships, graduate student training, medical residency training, psychology and social work training, as well as many opportunities for continuing medical education are part of the wide ranging academic options available at INT.

To give new impulse to translational research, it is crucial attracting medical doctors working in our Institute, and giving them the opportunity to receive training in cutting-edge research technologies. Our aim is to implement a system that will allow young physicians to gain direct experience in research and help the translation of laboratory discoveries into effective treatments for patients.

Since 1997 INT has partnered with the Open University (Milton Keynes, UK) to offer a PhD Programme for young graduates in scientific disciplines. During the course of their studies students conduct their experimental work under the supervision of experienced researchers, have access to modern laboratories and advanced technologies and benefit from a dedicated program of seminars. Academic quality of the educational programme is annually validated.

AS A COMPREHENSIVE CANCER CENTRE FOR EXCELLENCE, INT IS DEEPLY COMMITTED TO QUALITY EDUCATION AND TRAINING.

INT is a formal partner of the Università Statale degli Studi di Milano and hosts several professors of the Departments of Oncology and Hematoncology, including the Chairman, Medical Statistics and Biometry, Anesthesiology, and Pathology, with medical students and students from the medical biotechnology and nursingdegree; postgraduate training for the residencies of oncology, hematology, general surgery, radiotherapy, anesthesiology and intensive care are also provided.

INT IS A FORMAL PARTNER OF THE UNIVERSITÀ STATALE DEGLI STUDI DI MILANO

Young people have a natural curiosity towards the scientific rules governing the world.

To favour this attitude and increase their scientific knowledge, INT offers the possibility of brief stages to high school students for visiting laboratories, meeting INT researchers, learning importance of new technologies for advance in oncology research.

INT OFFERS THE POSSIBILITY OF BRIEF STAGES TO HIGH SCHOOL STUDENTS

SCHOLARLY OUTPUT

PUBLICATION AND IF BY DEPARTMENT

	Total N. Publication	IF	N. publications as first, last, corresponding author	IF
2016				
Scientific Directorate	67	318,552	21	81,246
Preventive and Predictive Medicine	151	867,150	25	117,272
Experimental Oncology and Molecular Medicine	117	515,478	66	292,838
Surgery	172	811,260	77	293,473
Hematology and Pediatric Onco-hematology	99	654,668	40	137,114
Medical Oncology	201	1176,060	94	396,277
Aneshesia, Intensive Care, Pain Therapy, and Palliative Care	33	146,114	11	60,825
Pathology and Laboratory Medicine	89	393,448	16	61,487
Diagnostic Imaging and Radiotherapy	83	298,147	23	56,102
Medica Directorate	13	33,398	1	1,071
2017				
Scientific Directorate	19	82,788	3	18,731
Research	224	1403,616	57	276,292
DRAST	98	495,138	40	188,396
Surgery	192	1011,732	90	390,364
Medical Oncology and Hematology	295	2474,967	133	701,796
Critical and Support Area	33	121,633	10	38,293
Pathology	85	339,038	16	60,917
Diagnostic Imaging and Radiotherapy	78	402,565	19	46,387
Medica Directorate	7	23,566	0	0

SELECTED PAPERS

2016

1

Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: A retrospective analysis

(Callegaro D. et al, Lancet Oncology 2016)

We have developed and externally validated two prediction nomograms representing reliable prognostic methods that can be used to predict overall survival and distant metastases in patients after surgical resection of soft-tissue sarcoma of the extremities. These nomograms can be offered to clinicians to improve their abilities to assess patient prognosis, strengthen the prognosis-based decision making, enhance patient stratification, and inform patients in the clinic.

2

Prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients: The MITO 15 trial

(Lorusso D. et al, Annal of Oncology 2016)

In the context of a prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients (The MITO 15 trial) our data confirmed that the signature of 'repeated platinum sensitivity' identifies patients highly responsive to trabectedin. In this setting, the activity of trabectedin seems comparable to what could be obtained using platinum compounds and the drug may represent a valuable alternative option in patients who present contraindication to receive platinum.

3

Development and validation of a microRNA-based signature (MiROvaR) to predict early relapse or progression of epithelial ovarian cancer: a cohort study

(Bagnoli M. et al, Lancet Oncology 2016)

We identified 35 miRNAs predicting risk of progression or relapse and used them to create a prognostic model, the 35-miRNA-based predictor of Risk of Ovarian Cancer Relapse or progression (MiROvaR). MiROvaR is a potential predictor of epithelial ovarian cancer progression and has prognostic value independent of relevant clinical covariates. MiROvaR warrants further investigation for the development of a clinical-grade prognostic assay.

4

MET-Driven Resistance to Dual EGFR and BRAF Blockade May Be Overcome by Switching from EGFR to MET Inhibition in BRAF-Mutated Colorectal Cancer.

(Pietrantonio F. et al, Cancer Discovery 2016)

Our studies identified -clinically and preclinically- MET amplification as a new mechanism of resistance to EGFR and BRAF dual/triple block combinations in BRAF-mutated colorectal cancer. Switching from EGFR to MET inhibition, while maintaining BRAF inhibition, resulted in clinical benefit after the occurrence of MET-driven acquired resi stance. We believe that specific targeting of MET-driven resistance to dual EGFR and BRAF block may lead to the design of biomarker-driven trials of second-line targeted therapy.

5

Subtype-specific metagene-based prediction of outcome after neoadjuvant and adjuvant treatment in breast cancer

(Callari M. et al, Clinical Cancer Research 2016)

We developed metagene-based predictors (linked to proliferation, ER-related genes, and immune response) able to define low and high risk of relapse after adjuvant/neoadjuvant therapy in breast cancer. In triple-negative breast cancer an immune-related metagene associated with prognosis and benefit from chemotherapy was identified, reinforcing the rational for testing a combination of immunomodulating agents and chemotherapy in this subset of highly aggressive tumors. Clinical trials enrolling only these patients would reduce the overtreatment and increase the chance of demonstrating a clinical meaningful benefit.

6

Functional genomics uncover the biology behind the responsiveness of head and neck squamous cell cancer patients to cetuximab

(Bossi P. et al, Clinical Cancer Research 2016)

Our study first specifically investigates cetuximab/platinum resistance in head and neck squamous cell carcinoma patients with recurrent-metastatic disease (RM-HNSCC) and illustrates the feasibility of gene expression profiling of pretreatment tumor to identify candidate biomarkers of response to anti-EGFR treatment in this subset of patients. Our data uncover the biology behind response to platinum-based chemotherapy plus cetuximab in RM-HNSCC cancer and may have translational implications improving treatment selection.

7

TNF-related apoptosis-inducing ligand (trail)-armed exosomes deliver proapoptotic signals to tumor site

(Rivoltini L. et al, Clinical Cancer Research 2016)

We investigated the ability of membrane TRAIL-armed exosomes to deliver proapoptotic signals to cancer cells and mediate growth inhibition in different tumor models. TRAIL-armed exosomes can induce apoptosis in cancer cells and control tumor progression in vivo. Therapeutic efficacy was particularly evident in intratumor setting, while depended on tumor model upon systemic administration. Thanks to their ability to deliver multiple signals, exosomes thus represent a promising therapeutic tool in cancer.

8

NFATc2 is an intrinsic regulator of melanoma dedifferentiation.

(Perotti V. et al, Clinical Cancer Research 2016)

In this study, we identify NFATc2 as major intrinsic regulator of human melanoma dedifferentiation, a process implicated in resistance to chemotherapy, target therapy and immunotherapy. By different approaches, we found that the expression of NFATc2 is associated with a $CD271^{+}$ dedifferentiated phenotype which, in turn, is controlled by NFATc2 through a pathway that involves mTNF-α, c-myc and Brn2. Moreover, we show that targeting of NFATc2 improves tumor recognition by MDA-specific cytotoxic T cells. Taken together, our results suggest that the expression of NFATc2 promotes melanoma dedifferentiation and immune escape.

SELECTED PAPERS

2016

9

miR-9 and miR-200 regulate PDGFRβ-mediated endothelial differentiation of tumor cells in triple-negative breast cancer

(D'Ippolito E. et al, Cancer Research 2016)

We investigated the role of miRNAs as a therapeutic approach to inhibit PDGFRβ-mediated vasculogenic properties of triple-negative breast cancer (TNBC), focusing on miR-9 and miR-200. Our results demonstrate that miR-9 and miR-200 play opposite roles in the regulation of the vasculogenic ability of TNBC, acting as facilitator and suppressor of PDGFRβ, respectively. Moreover, our data support the possibility to therapeutically exploit miR-9 and miR-200 to inhibit the process of vascular lacunae formation in TNBC.

10

Mesenchymal Transition of High-Grade Breast Carcinomas Depends on Extracellular Matrix Control of Myeloid Suppressor Cell Activity

(Sangaletti S. et al, Cell Reports 2016)

Biological and clinical characteristics of breast cancer are determined by both tumor cells and normal cells belonging to the immune system. The last together with the extracellular matrix (ECM) contribute to form the tumor microenvironment. Informations about the prognosis of high grade breast tumors can be obtained by studying the expression profile of genes encoding for ECM proteins. In this context, we have shown that extracellular matrix proteins can influence the recruitment and activity of myeloid cells to support tumor growth and aggressiveness. Additionally, we demonstrated the efficacy of aminobiphosphonates, drugs clinically employed in the treatment of osteoporosis, in blocking myeloid cell functions and consequently improving/restoring response to chemotherapy.

11

Survival of European adolescents and young adults diagnosed with cancer in 2000–07: population-based data from EUROCARE-5

(Trama A. et al, Lancet Oncology 2016)

Notwithstanding the encouraging results for some cancers, and overall, we showed poorer survival in Adolescents and Young Adults (AYAs) than in children for the eight important cancers. Recent European initiatives to improve outcomes in AYAs might reduce the survival gap between children and AYAs, but this reduction can only be verified by future population-based studies.

12

Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma

(Massimino M. et al, Neuro-Oncology 2016)

In a national multi-institutional collaboration, with the largest sample of ependymoma patients in a prospective trial to date (the second prospective AIEOP protocol for pediatric intracranial ependymoma), we have demonstrated the feasibility of multiple surgical procedures followed by a novel radiotherapeutic (RT) approach, with a trend to outcome amelioration in children with residual disease, a patient group that carries a poor prognosis.

2017

13

Impact of home enteral nutrition in malnourished patients with upper gastrointestinal cancer: A multicentre randomised clinical trial.

(Gavazzi C. et al, European Journal of Cancer 2016)

Randomised trials aimed at investigating the effects of Home Hnteral Nutrition (HEN) in post-surgical patients with GI cancer are lacking. Our study comparing HEN and counselling in limiting weight loss during oncologic treatment indicates that HEN is a simple and feasible treatment to support malnourished patients with upper GI cancer after major surgery and during chemotherapy in order to limit further weight loss.

1

Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study

(Gatta G. et al, Lancet Oncology, 2017)

Our study benefits from the largest pool of population-based registries to estimate incidence and survival of about 200 rare cancers. Incidence trends can be explained by changes in known risk factors, improved diagnosis, and registration problems. Survival could be improved by early diagnosis, new treatments, and improved case management. The centralisation of treatment could be improved in the seven European countries we studied.

2

Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

(Gronchi A. et al, Lancet Oncology, 2017)

In a population of patients with high-risk soft-tissue sarcoma, we did not show any benefit of a neoadjuvant histotype-tailored chemotherapy regimen over the standard chemotherapy regimen. The benefit seen with the standard chemotherapy regimen suggests that this benefit might be the added value of neoadjuvant chemotherapy itself in patients with high-risk soft-tissue sarcoma.

3

Trabectedin overrides osteosarcoma differentiative block and reprograms the tumor immune environment enabling effective combination with immune checkpoint inhibitors

(Ratti C. et al, Clinical Cancer Research, 2017)

These results demonstrate the therapeutic efficacy of trabectedin in osteosarcoma treatment, unveiling its multiple activities and providing a solid rationale for its combination with immune checkpoint inhibitors.

SELECTED PAPERS

2017

4

High-dose chemotherapy followed by autologous transplantation may overcome the poor prognosis of diffuse large B-cell lymphoma patients with MYC/BCL2 co-expression

(Maura F. et al, Blood Cancer Journal, 2017)

Overall, results of this study suggest that standard high-dose therapy and final transplant consolidation may abolish the poor prognostic value associated with MYC/BCL2 co-expression among young and/or fit diffuse large B-cell lymphoma patients both in first line and first relapse.

5

Baseline and postoperative C-reactive protein levels predict mortality in operable lung cancer

(Pastorino U. et al, European Journal of Cancer, 2017)

Baseline and postoperative C-reactive protein (CRP) levels predict immediate and long-term mortality in all stages of operable lung cancer. Patients with higher CRP levels could be candidate to randomised adjuvant trials with anti-inflammatory agents.

6

Heterogeneity of acquired resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer

(Pietrantonio F. et al, Clinical Cancer Research, 2017)

Our results indicate that it may be extremely challenging to target the complex landscape of molecular heterogeneity associated with emergence of resistance to targeted therapies in patients with metastatic colorectal cancer.

7

Patient-derived solitary fibrous tumour xenografts predict high sensitivity to doxorubicin/dacarbazine combination confirmed in the clinic and highlight the potential effectiveness of trabectedin or eribulin against this tumour

(Stacchiotti S. et al, European Journal of Cancer, 2017)

Doxorubicin plus temozolomide and dacarbazine (DTIC) combination was effective in our two Dedifferentiated Solitary fibrous tumour (D-SFT) mice models and appeared to be active also in the clinic, especially in high-grade D-SFT patients. Among additional drugs tested in the patient-derived xenograft (PDXs), trabectedin and eribulin were highly effective, providing a rational to test these drugs in D-SFT patients.

8

Early effector T lymphocytes coexpress multiple inhibitory receptors in primary non-small cell lung cancer

(Tassi E. et al, Cancer Research, 2017)

The identification of EECs (Early Effector Cells) marked by inhibitory receptor expression at tumor sites will enable investigations of early stages of adaptive antitumor immunity, as well as support the rationale for administering immunotherapy in early-stage non-small cell lung cancer.

9

Fentanyl sublingual tablets versus subcutaneous morphine for the management of severe cancer pain episodes in patients receiving opioid treatment: A double-blind, randomized, noninferiority trial

(Zecca E. et al, Journal of Clinical Oncology, 2017)

This trial did not show noninferiority of FST versus SCM within the chosen NIm. Both treatments were safe, and patients preferred the sublingual route of administration. FST provides analgesia with modest to moderate increased risk of lower efficacy compared with SCM.

10

Pazopanib in advanced germ cell tumors after chemotherapy failure: Results of the open-label, single-arm, phase 2 Pazotest trial

(Necchi A. et al, Annals of Oncology, 2017)

Despite pazopanib showed potent but short-lived activity in refractory germ cell tumor (GCT), long-term survival was obtained in a proportion of treated patients. According to the kinetics of pazopanib activity, this drug may be investigated in less pre-treated patients as an optimal bridging therapy preceding and/or combined with salvage chemotherapy.

11

Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition Cancer Staging Manual

(Gershenwald J.E. et al for members of the American Joint Committee on Cancer Melanoma Expert Panel and the International Melanoma Database and Discovery Platform, CA: a Cancer Journal for Clinicians, 2017)

The eighth edition of the American Joint Committee on Cancer Melanoma Staging System provides an updated framework for the classification and staging of patients with cutaneous melanoma.

RESEARCH FUNDING

	Projects started 2016	
	Nr	€
Private foundation – Grant	18	€ 4,477,814.96
AIRC – Italian Association for Cancer Research	13	€ 3,565,999.96
CARIPLO Foundation	3	€ 690,815.00
AIOM – Italian Association of Medical Oncology	1	€ 100,000.00
Giovanni Celeghin Foundation	1	€ 121,000.00
Public authority – International Grant	5	€ 2,426,430.70
European Commission	4	€ 2,176,430.70
Ministry of Health (TRANSCAN)	1	€ 250,000.00
Public authority – National Grant	8	€ 1,816,098.00
Ministry of Health (APPLIED RESEARCH)	6	€ 1,656,598.00
Regione Lombardia, Cariplo Foundation	1	€ 95,000.00
LILT – Italian League Against Cancer	1	€ 64,500.00
Private foundation - Fellowship	14	€ 499,000.00
FUV - Umberto Veronesi Foundation	9	€ 243,000.00
AIRC - Italian Association for Cancer Research, FIRC – Foundation for Italian Cancer Research	3	€ 213,000.00
Michelangelo Foundation	1	€ 18,000.00
Pezcoller Foundation	1	€ 25,000.00
Private Foundation or Entity – Other projects	6	€ 601,000.00
Italo Monzino Foundation	2	€ 440,000.00
AIL – Italian Association Against Leukemia, Lymphoma and Myeloma Onlus	1	€ 36,000.00
Rocca Foundation	1	€ 70,000.00
Barilla S.p.A.	1	€ 40,000.00
Italian Association GIST Onlus	1	€ 15,000.00
Public Authority – Other projects	15	€ 520,057.60
LILT - Italian League Against Cancer	12	€ 479,057.60
Local Health Authorities	1	€ 24,000.00
Italian municipalities	1	€ 8,000.00
Universities	1	€ 9,000.00
Total	66	€ 10,340,401.26

	Projects started 2017	
	Nr	€
Private foundation – Grant	7	€ 4,037,554.25
AIRC – Italian Association for Cancer Research	7	€ 4,037,554.25
Public authority – International Grant	6	€ 1,249,424.84
European Commission	3	€ 335,999.32
Ministry of Health (TRANSCAN)	2	€ 871,000.00
NIH - National Institutes of Health	1	€ 42,425.52
Public authority – National Grant	1	€ 330,239.00
Ministry of Health (APPLIED RESEARCH)	1	€ 330,239.00
Private foundation - Fellowship	10	€ 319,000.00
FUV - Umberto Veronesi Foundation	7	€ 189,000.00
AIRC - Italian Association for Cancer Research, FIRC – Foundation for Italian Cancer Research	2	€ 100,000.00
Cook Ireland Ltd	1	€ 30,000.00
Private Foundation or Entity – Other projects	1	€ 15,000.00
Patrizia Revello Association	1	€ 15,000.00
Public Authority – Other projects	10	€ 396,300.00
LILT - Italian League Against Cancer	10	€ 396,300.00
Total	35	€ 6,347,518.09

CLINICAL RESEARCH ACTIVITY

Data are collected, evaluated and summarized by the Scientific Technical Secretary of the Ethics Committee according to the administrative monitoring process in place at the end of December of each year.

CLINICAL STUDIES ONGOING*

2016		2017
19	Registry	18
395	Experimental studies	421
230	Observational studies	217
644	Total	656

CLINICAL STUDIES ONGOING* BY SPONSOR

2016		2017
422	No Profit	418
222	Profit	238
644	Total	656

* at least 1 patient enrolled or in follow-up

CLINICAL STUDIES ONGOING BY DESIGN AND SPONSOR

2016				2017		
Total	No Profit	Profit	Study design	Profit	No Profit	Total
45	45		Observational biological		40	40
18	8	10	Observational prospective – drug	11	9	20
88	87	1	Observational prospective – no drug	2	87	89
62	59	3	Observational retrospective – no drug	1	52	53
17	15	2	Observational retrospective –drug	1	13	14
19	19		Registry		19	19
6	4	2	Experimental - device	3	4	7
353	150	203	Experimental - drug	219	160	379
36	35	1	Experimental - no drug	1	34	35
644	422	222	Total	238	418	656

CLINICAL STUDIES STARTED BY DESIGN AND SPONSOR*

2016				2017		
Total	No Profit	Profit	Study design	Profit	No Profit	Total
10	10		Observational biological		7	7
7	3	4	Observational prospective – drug	3	1	4
22	21	1	Observational prospective – no drug	1	21	22
36	34	2	Observational retrospective – no drug	1	19	20
8	7	1	Observational retrospective –drug		4	4
2	2		Registry		2	2
2	1	1	Experimental - device	1	1	2
70	19	51	Experimental - drug	51	23	74
9	8	1	Experimental - no drug		7	7
166	105	61	Total	57	85	142

* at least 1 patient included

CLINICAL RESEARCH ACTIVITY

CLINICAL STUDIES COMPLETED BY DESIGN AND SPONSOR

2016				2017		
Total	No Profit	Profit	Study design	Profit	No Profit	Total
12	12		Observational biological		11	11
2		2	Observational prospective – drug	3		3
20	20		Observational prospective – no drug	1	18	19
29	26	3	Observational retrospective – no drug		23	23
7	6	1	Observational retrospective –drug	1	7	8
3	3		Registry			
1	1		Experimental - device	1	2	3
48	13	35	Experimental - drug	36	25	61
8	8		Experimental - no drug		6	6
130	89	41	Total	42	92	134

EXPERIMENTAL DRUG STUDIES ONGOING BY PHASE AND SPONSOR

2016				2017		
Total	No Profit	Profit	Phase	Profit	No Profit	Total
21		21	I	23		23
27	11	16	I/II	20	9	29
1		1	I/III	3		3
145	88	57	II	57	97	154
6	6		II/III		6	6
142	38	104	III	112	42	154
11	7	4	IV	4	6	10
353	150	203	Total	219	160	379

NUMBER OF PATIENTS ENROLLED AND TOTALS

2016			2017	
Total patients	Patients 2016	Study design	Patients 2017	Total patients
6495	3283	Observational biological	1053	5335
703	151	Observational prospective – drug	60	748
18356	2901	Observational prospective – no drug	3080	19704
62309	5534	Observational retrospective – no drug	2096	58492
612	361	Observational retrospective –drug	180	407
34758	9752	Registry	9360	44037
138	17	Experimental - device	71	168
9237	1739	Experimental - drug	1930	8358
8002	705	Experimental - no drug	2920	5668
140610	24443	Total	20750	142917

NUMBER OF PATIENTS ENROLLED AND TOTAL PATIENTS BY PHASE

2016			2017	
Total patients	Patients 2016	Phase	Patients 2017	Total patients
381	67	I	50	309
246	129	I/II	129	366
4	4	I/III	9	13
2502	476	II	423	2594
69	15	II/III	12	81
3687	952	III	1280	4870
2348	96	IV	27	125
9237	1739	Total	1930	8358

CLINICAL RESEARCH ACTIVITY

CLINICAL STUDIES WITH INT AS SPONSOR, BY TYPE AND DESIGN

2016			2017	
Total studies ongoing	Started 2016	Study design	Started 2017	Total studies ongoing
36	8	Observational biological	5	31
4	1	Observational prospective – drug	1	5
49	15	Observational prospective – no drug	14	52
46	31	Observational retrospective – no drug	13	39
6	1	Observational retrospective –drug	3	7
9		Registry	1	8
2		Experimental - device	1	2
51	3	Experimental - drug	7	51
24	6	Experimental - no drug	3	21
227	65	Total	48	216

ETHICS COMMITTEE

The institutional Ethics Committee reviews all new clinical studies submitted by investigators and previously approved by the Scientific Institutional Review Board.
The Committee was established in 1973.

In the years 2016-2017, 432 new studies were submitted to the Ethics Committee for approval: 113 in 2016 e 132 in 2017 were interventional trials, of which respectively 74 and 94 were sponsored by pharmaceutical companies and 39 and 38 were investigator-driven; 95 in 2016 and 92 in 2017 were observational, of which a total of 12 were sponsored by pharmaceutical companies and 175 were investigator-driven.

The median time from submission to Ethics Committee discussion was in the range of one month (28 days), thus paralleling the satisfactory timelines of previous years.

During 2016-2017, a total of 786 studies were active: 325 studies were enrolling, 197 studies were closed to accrual and 264 ended during the years.
A total of 147,699 cases are involved, of which 45,193 new patients in the two years; most of them (37,811) involved in observational studies and the others (7,382) in interventional studies (1,276 patients in industry-sponsored trials and 6,106 in investigator-driven trials).

CHAIRMAN
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SCIENTIFIC SECRETARIAT
Paolo G. Casali, Bianca M. Francucci

ADMINISTRATIVES
Raffaella Didoné, Patrizia Polo, Emiliano Stendardo, Cristina Rizzo

SCIENTIFIC REPORT

2016-2017

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Fondazione IRCCS Istituto Nazionale dei Tumori

Via G. Venezian, 1 - 20133 Milan - Italy
Scientific Directorate
Tel. +39 02 2390 2300
Fax +39 02 2390 3141
direzionescientifica@istitutotumori.mi.it

For more ditails see web site
www.istitutotumori.mi.it