SPEAKERS PRESENTATION

Future perspectives in ovarian cancer research

Stockholm 16-17 November 2022

Aneheim, Emma Docent (Associate Professor) • Sweden

Fellows: Towards Curing Ovarian Carcinoma with Targeted Alpha Therapy with Targeted Alpha Therapy

Affiliation: University of Gothenburg, the Sahlgrenska Academy, Department of Medical Radiation Sciences / Sahlgrenska University Hospital

Research Area: Different aspects of Targeted Alpha Therapy (TAT) of disseminated cancer with the radioactive alpha particle emitting nuclide astatine-211. Especially work towards clinical application of intraperitoneal radio-immunotherapy of ovarian cancer including radiopharmaceutical production and automation efforts, pretargeted radioimmunotherapy for systemic applications of TAT with astatine and basic astatine chemistry.

Anglesio, Michael Assistant Professor • Canada

Biomarkers and in vitro models to differentiate subtypes of ovarian cancer histologies

Affiliation (primary): University of British Columbia, Department of Obstetrics and Gynaecology, Div of Gynecologic Oncology/Div of Gynecologic Specialties

Other Affiliations: (i) University of British Columbia, Vancouver General Hospital, and BC Cancer. British Columbia's Gynecological Cancer Research Team (OVCARE); (ii) BC Women's Hospital + Health Centre, Women's Health Research Institute; (iii) University of British Columbia and Vancouver Coastal Health Research Institute, Department of Pathology and Laboratory Medicine, Molecular and Advanced Pathology Core (MAPcore).

Research Area: Dr. Anglesio trained at McGIll University, the University of British Columbia (UBC), and the Peter MacCallum Cancer Centre. Dr. Anglesio has been supervising students, and mentoring junior researchers and visiting scientists in Vancouver since 2010. He has been a faculty member at UBC since 2017. His work has centered on further defining subtypes of ovarian carcinoma following evidence that ovarian cancers are a collection of distinct disease. Most recently he has focused on uncovering the mechanisms through which endometriosis may become malignant and progress into either clear cell or endometrioid ovarian carcinoma.

Balkwill, Frances Professor of Cancer Biology. Fellow of the Academy of Medical Sciences, Honorary Fellowship of the British Science Association. Deputy Centre Lead, Group Leader, Research Theme Lead • UK

Deconstruction and Reconstruction of the ovarian cancer microenvironment

Frances Balkwill is Professor of Cancer Biology at Barts Cancer Institute, Queen Mary University of London and Deputy Lead for the Centre for Tumour Microenvironment. She is especially interested in translating knowledge of cancer biology into new biological treatments for cancer. Much of her work focuses on the tumour microenvironment of ovarian cancer. After publishing a multi-level profile of the human ovarian cancer microenvironment, her lab developed a platform of new mouse models as well as human multi-cellular tissue culture models. They are now using these to research biological therapies that may prevent relapse and increase patient survival.

Fran is Director of the Centre of the Cell, a biomedical science centre for children, educational website and outreach project in East London. There have been more than 230,000 participants in Centre of the Cell activities since opening in September 2009. Together with illustrator Mic Rolph, Fran has also produced thirteen science books for children on cell and molecular biology with titles such as Enjoy Your Cells, The Egg and Sperm Raceand You, Me and HIV. These books have been translated into at least twelve foreign languages with over half a million copies sold worldwide.

Fran serves on CRUK and ERC grant committees. She is a Trustee of the charity Blood Cancer UK and chairs the Research Advisory Committee of Prostate Cancer UK.

Brenton, James PhD FRCP. Professor of Ovarian Cancer Medicine and Senior Group Leader, Cancer Research UK Cambridge Institute, University of Cambridge • UK

Molecular and clinical heterogeneity of high-grade serous ovarian cancer

Affiliations: Co-director Cancer Research UK Cambridge Centre Ovarian Cancer Programme and Co-director, The Mark Foundation Institute for Integrated Cancer Medicine.

National lead for the ovarian cancer domain in the Genomics England Clinical Interpretation Partnership and Genomics England Genomics Medicine Centre

Research area: High-grade serous ovarian carcinomas HGSC have highly complex genomic profiles with few targetable mutations. This marked chromosomal instability (CIN) has impeded molecular classification and the development of precision medicine approaches. We hypothesised that patterns of copy number aberrations might specifically identify different mutational processes on the HGSC genome. We have developed copy number signatures that provide a systematic framework to comprehensively characterize the diversity, extent and origins of CIN and are carrying out pre-clinical and clinical studies that indicate how copy number signatures can provide disease stratification and treatment prediction in HGSC.

Drapkin, Ronny MD, PhD. Director, Ovarian Cancer Research Center. Director, Gynecologic Cancer Research, Basser Center for BRCA. Franklin Payne Associate Professor of Pathology in Obstetrics & Gynecology • USA

Modeling the origins of ovarian cancer and the impact of a novel tumor microenvironment component

Einstein, Gillian Adjunct Scientist, Women's College Research Institute. Associate Professor of Psychology, University of Toronto. Associate Professor of Dalla Lana School of Public Health, University of Toronto • Canada and Sweden

Cognitive and other side effects of prophylactic surgery

Gillian Einstein is The Wilfred and Joyce Posluns Chair in Women's Brain Health and Aging, Professor of Psychology at the University of Toronto and Guest Professor of Gender and Health at Linköping University in Linköping, Sweden. She is a board member of the International Gender Medicine Society, editor for Frontiers in Neuroendocrinology and Frontiers in Endocrinology and Neuroscience special section on Neuroendocrinology, Chair of the Canadian Institutes of Health's Institute of Gender and Health Advisory Board, and leads the Women, Sex, Gender, and Dementia Cross-Cutting Program for the Canadian Consortium on Neurodegeneration and Aging. She is the founder and President of the Canadian Organization of Gender and Sex (COGS) Research.

Reserach Area: She has published in vision, mood, chronic pain, and the effects of ovarian hormones on women's brain health. Her research focus is on Why more women than men have Alzheimer's disease and what tips the balance at midlife. She is currently funded by Cancerfonden, the Canadian Insitutes of Health Research, The Women's Brain Health Initiative, The Centre for Aging + Brain Health Innovation (CABHI), the Ontario Brain Institute, and Brain Canada to study the cognitive and brain effects of early life ovarian removal and the long-term effects of gender affirming hormone therapy in aging trans women.

Professor Einstein uses a method she devised called, "Situated Neuroscience" with a combination of qualitative, quantitative, and physiological methods (Very Mixed Methods) to explore how both sex and gender mediate women's brain health. Using qualitative interviewing, large data sets, neuroimaging, biomarker measures, and neuropsychology she tries to understand how the social becomes biological – or, how the world writes on the body.

Färkkilä, Anniina MD PhD, Associate Professor in Translational Gynecologic Oncology Principal Investigator, Academy of Finland Clinical research Fellow • Finland

Genomic and immune profiling for predictivebiomarkers

Anniina Färkkilä, MD PhD, is an Associate professor and Specialist of obstetrics and gynecology at the University of Helsinki and Helsinki University Hospital, Finland. She is a board member at the NSGO, and the translational working groups of ENGOT and GCIG. In 2018 she was awarded the Seth Wichmann award by the Finnish Gynecologic Society, and in 2022 the Eero Saksela award by the Finnish Cancer Institute.

Reserach Area: Dr Färkkilä´s research currently focus on understanding the complexity and cell-cell interactions in the tumor microenvironment using genomics, highly multiplexed imaging, advanced bioinformatics, and functional models in ovarian cancer.

Falconer, Henrik Karolinska University Hospital and Karolinska Institutet, Department of Pelvic Cancer and the Department of Women's and Children's Health • Sweden

Pro-Con discussion on risk-reducing surgery in hereditary and non-hereditary Ovarian Cancer – Pro-Con discussion

Associate Professor Henrik Falconer is Head of Gynecologic oncology at Karolinska University Hospital, Sweden.

Reserach Area: Dr Falconers research is currently focused on cancer epidemiology and clinical trials in robotic surgery. He is the Principal Investigator for the international RACC-trial (Robot-assisted Approach to Cervical Cancer) and has been working with many aspects of robotic surgery for more than 10 years with a special interest in education. Dr Falconer is the chairman of the national guidelines committee for cervical cancer and the treasurer of SERGS.

Jonkers, Jos Professor of Molecular experimental ontogenetics and cancer therapeutics. Head of Division of Molecular Pathology at Netherlands Cancer institute • Netherlands

Mouse models for BRCA1 associated tumorigenesis and genomic instability

Jos Jonkers performed his PhD and postdoctoral research in the group of Dr. Anton Berns at the Netherlands Cancer Institute (NKI). Following his second postdoc in the group of Dr Allan Bradley at the Wellcome Sanger Institute, he started his own research group at the NKI in 2003. His group (www.nki.nl/research/research-groups/jos-jonkers) studies human breast cancer using genetically engineered mouse models and patient-derived xenograft models. He is currently a Senior Group Leader in the Division of Molecular Pathology at the NKI, Affiliate Professor of Molecular Experimental Oncogenetics and Cancer Therapeutics at Leiden University, and elected member of the European Molecular Biology Organization (EMBO).

Levanon, Keren MD, PhD, Head of the Ovaria Cancer Research Lab and senior medical oncologist Sheba Cancer Center • Israel

Proximal liquid biopsy for early detection of ovarian cancer

Research Area: My reserach focus on the origin of ovarian cancer and development of biomarkers. This includes early-detection biomarkers, mainly based on proximal liquid biopsies, and predictive biomarkers for individualized first line treatment. I am also a practicing senior medical oncologist, treating women with breast and gynecological malignancies.

Lindemann, Kristina Head of research, Associate Professor; PhD, MD • Norway

Unmet needs in end of life care in ovarian cancer patients

Associate professor Kristina Lindemann is a staff specialist and head of research at the Department of gynecological oncology at Oslo University Hospital, Norway. She leads the National advisory unit of gynecological oncology and is the Deputy Medical Director of NSGO-CTU (Nordic Society of Gynaecological Oncology-CTU).

She defended her PhD on "Obesity and the risk of endometrial cancer" in 2010 and has completed The Global Clinical Scholars Research Training Program at Harvard Medical School. Between 2015 and 2016 she joined the Crown Princess Mary Cancer Centre, Westmead, and the NHMRC Clinical Trials Centre in Sydney for a fellowship.

In 2022 she is Principal Investigator of >10 clinical trials and is lead PI of the PEACE trial, a multicenter international trial in end-of-life care. Her research focus is to improve patient care through translating knowledge in cancer biology, drug development and supportive care.

Magalhaes, Isabelle PhD, Associate Professor • Sweden

Fellows: "Chimeric antigen receptor T cell therapy for the treatment of advanced ovarian cancer"

Isabelle Magalhaes received her PhD in Immunobiology in 2009 (Karolinska Institutet), and is Docent in Immunology since 2021.

Research Area: Interests focused on T cells including T cell subsets such as CD8alphaalpha+ T cells and MAIT cells and since 2015 more particularly on chimeric antigen receptor (CAR) T cells for the treatment of cancer.

Manchanda, Ranjit Professor of Gynaecological Oncology, Wolfson Institute of Population Health, QMUL, London, UK. Consultant Gynaecological Oncologist, Barts Health NHS Trust, London, UK. Honorary Professor, Department of Health Services Research, London School of Hygiene & Tropical Medicine, London, UK. Integrated Academic Training Programme Director, London Specialty School of Obs & Gynae, Health Education England. Specialty Research Lead for Gynaecological Cancer, NIHR, North Thames Clinical Research Network. NHS Innovation Accelerator (NIA) Alumnus. Distinguished Infosys Chair in Oncology, AIIMS • India

Prevention in hereditary and non-hereditary Ovarian Cancer

Select positions:
Co-Lead Cancer Prevention Unit, Wolfson Institute of Population Health, QMUL, London, UK
Co-Lead for Cancer Prevention (Theme-1), Barts CRUK Cancer Centre
Topic Advisor/ Clinical Lead NICE Familial Ovarian Cancer Guideline
Member National Cancer Programme Early Diagnosis Task & Finish group
Lead Women's Precision Prevention Service, Barts Health NHS Trust

Rsearch Area: Targeted Precision Prevention including, population-based germline testing, mainstreaming genetic testing and precision medicine approaches for risk prediction, stratification, targeted screening & targeted cancer prevention, along with economic evaluation issues related to these areas of research.

PI: GCaPPS, PROTECTOR, PROMISE Pilot, SIGNPOST, RRESDO, SURAKSHA, UKCOGS, DETECT-2, PROTECT-C, PRESCORES, JHCR & Economic evaluation studies

Murtaza, Muhammed Associate Professor of Surgery and Associate Director of Center for Human Genomics and Precision Medicine, University of Wisconsin-Madison • USA

Target and genome-wide analysis approaches for early detection using liquid biopsises

Speaker bio: Dr. Muhammed Murtaza is an Associate Professor in the Division of Surgical Oncology at University of Wisconsin-Madison. He leads a laboratory research program based in the Center for Human Genomics and Precision Medicine at UW School of Medicine and Public Health. Prior to this position, he was a faculty member at Translational Genomics Research Institute in Phoenix, AZ and at Mayo Clinic Arizona. Murtaza holds a PhD from University of Cambridge (Cancer Research UK Cambridge Institute) and an MBBS from Aga Khan University in Karachi, Pakistan. Dr. Murtaza's research is focused on leveraging genomics and computational biology to bridge diagnostic gaps and improve outcomes for cancer patients. Funded by multiple grants from the National Institute of Health, the lab investigates new strategies for improving accuracy of and access to circulating tumor DNA analysis for early detection, treatment response monitoring, and for tracking and leveraging cancer evolution.

Research Area: Development of computational and molecular methods to improve liquid biopsies for cancer diagnostics including early detection and minimal residual disease detection. Recent work includes development of genomewide analysis of fragment ends (GALYFRE) as a potential approach for improving cancer detection and monitoring using cell-free DNA samples from plasma and urine (Markus et al. Science Translational Medicine 2021 and Budhraja et al. medRxiv 2022).

Oza, Amit Chief, Division of Medical Oncology & Hematology, Medical Director of the Cancer Clinical Research Unit at Princess Margaret Cancer Centre (PM). Co-Director of the Drug Development Program at PM, Scientist at the Ontario Cancer Institute, and Professor of Medicine at University of Toronto. • Canada

Ovarian cancer: therapeutic targeting of the Hallmarks of cancer in relation to subtype

Opportunities and obstacles for immune therapy in ovarian cancer

Dr. Oza has been PI and co-investigator in >100 phase I, II and III trials for gynecological cancer and advanced colorectal malignancies. He is the past co-chair of the National Cancer Institute Gynecologic Caner Steering Committee, and the current Chair of the international Gynecologic Cancer InterGroup (GCIG). Under his direction, the gynecology group is one of the largest ovarian cancer (OC) clinical trials groups consistently accruing >30% of all patients seen onto clinical trials (>150/yr) at PM.

Research Area: The group has participated or led seminal studies in gynecologic cancers that have led to the approval or use of targeted agents such as PARP inhibitors (olaparib, niraparib) and anti-angiogenic agents (bevacizumab) internationally. Over the last decade he has been PI/co-PI of 19 grants from agencies such as the Canadian Cancer Society Research Institute, Canadian Institutes for Health Research, National Institutes of Health (NIH), Ontario Institute for Cancer Research, and the US Department of Defense. Over his career he has published >290 articles (all types) including Clinical Cancer Research (IF=10), JAMA Oncology (IF=20), New England Journal of Medicine (IF=79), Lancet Oncology (IF=36) and an invited seminar to CA: A Cancer Journal for Clinicians (IF=244).

Sahar Salehi MD, PhD, Docent in surgical gynecologic oncology. Karolinska University Hospital and Karolinska Institutet • Sweden

Fellows: Tumour and stroma responses to surgical trauma and anti-inflammatory anesthetics.

I'm a Senior consultant and surgical gynecologic oncologist, responsible for ovarian cancer surgery at Karolinska University Hospital.

Research Area: My research mainly pertains to the effect of surgery on short and long-term outcome in gynecologic malignancies with special focus on advanced ovarian cancer.

Strandell, Annika Associate professor in Obstetrics and Gynaecology at the Sahlgrenska Academy at the University of Gothenburg • Sweden

Pro-Con discussion on risk-reducing surgery in hereditary and non-hereditary Ovarian Cancer – Pro-Con discussion

Research Area: As a researcher and clinician within reproductive medicine, I have strongly recommended salpingectomy to patients with severe tubal disease, before undergoing in vitro fertilisation, to increase their chances of achieving pregnancy and live birth. Now my research is focusing on salpingectomy for another group of women, with the goal to reduce to risk of epithelial ovarian cancer. I am a grateful receiver of grants from the Swedish Cancer Society supporting two trials, HOPPSA and SALSTER, aiming at primary prevention of ovarian cancer.

Vorobyeva, Anzhelika PhD, Docent in Radionuclide-based molecular imaging at Uppsala University • Sweden

Fellows: Co-targeting of HER2 and EpCAM using novel types of targeting probes for theranostics of ovarian cancer"

Affiliation: Research Fellow with support of Cancerfonden in the group of Professor Vladimir Tolmachev at the Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Research Area: We are investigating the feasibility of using novel scaffold proteins (DARPins, affibody molecules and ADAPTs) for targeted cytotoxic therapy and radionuclide imaging of ovarian cancer. The current knowledge about tumor-targeting agents based on small protein scaffolds is very limited. We are studying their structure-property relationship to develop more effective and safe therapies. Together with initial selection and monitoring of response to therapy using PET or SPECT imaging, it forms a personalized theranostic approach to cancer treatment. Application of the developed targeted therapies could be envisioned for other types of cancer due to overexpression of these molecular targets in many cancers.

Weiderpass, Elisabete MD, MSc, PhD. Professor, Director, International Agency for Research on Cancer • Sweden

Risk factors for Ovarian Cancer

Dr Weiderpass is the Director of the International Agency for Research on Cancer, the specialized cancer agency of the World Health Organization. Dr Weiderpass is an expert in cancer epidemiology and cancer prevention.

Research Area: Dr Weiderpass previously served as Head of the Department of Research at the Cancer Registry of Norway, and of the Genetic Epidemiology Group at the Folkhälsan Research Center in Finland. She was a Professor of Medical Epidemiology at the Karolinska Institutet in Stockholm, Sweden, and a Professor of Cancer Epidemiology at the Arctic University of Norway.

Dr Weiderpass has authored over 1000 scientific publications in peer-reviewed journals.

Wennerberg, Krister Professor. Ph.D • Denmark

Organoid-based models for precision oncology and research

Krister Wennerberg is a Professor at the Biotech Research & Innovation Centre (BRIC), University of Copenhagen.

Research Area: Dr Wennerbergs research aim at understanding mechanisms of drug resistance and sensitivity in individual ovarian cancers. A particular interest is to map mechanisms by which subsets of cancer cells persist therapies and drive recurrence, which could allow for the identification of new stratified precision therapies. Key research efforts include:

- Develop improved in vitro experimental model systems, including organoids.
- Perform phenotypic and molecular analyses of the primary culture models.
- Building predictive models of drug resistance development and new treatment opportunities.

Uddin, Kazi Associate professor • Sweden

Fellows: Understanding the non-genetic mechanisms of therapy resistance

I am a Swedish Cancer Society Ovarian Cancer Fellow and an associate professor at Lund University Medical Faculty.

Research Area: My research mainly focuses on understanding the molecular mechanisms of therapy resistance. Particularly, we are interested in non-genetic mechanisms of therapy resistance. We use pharmacogenomics and machine learning to stratify drug sensitivity vs resistance, and biochemical tools to explain the underlying mechanisms in preclinical models of cancer.

Steering committee

Dahm Kähler, Pernilla Associate Professor Dept. Obstetrics and Gynecology Sahlgrenska Academy at University of Gothenburg, Gothenburg • Sweden

What is optimal Ovarian Cancer Surgery – When, How and to Whom?

Moderator

Associate professor Pernilla Dahm Kähler became a specialist in Obstetrics and Gynecology in 1999 and was the first certified Swedish subspecialist in gyne-oncologic surgery in 2005 and finished her PhD in 2006. She is the Head of Gyne-Oncology surgery at the Dept of Obstetrics and Gynecology at Sahlgrenska University Hospital and has been working intensively with optimizing gynaecological cancer surgery including centralization of advanced ovarian cancer. She is the national registry holder for the Swedish Quality Register for Gynecological Cancer, a member of the Swedish gynecologic cancer group and board member of national expert referral groups in gynecologic cancer.

Hedenfalk, Ingrid Professor • Sweden

Moderator

Affiliation: Lund University, Department of Clinical Sciences Lund, Division of Oncology, Breast and Ovarian Cancer Genomics group

Research Area: We are interested in elucidating the cell-of-origin, molecular landscapes and microenvironmental impact associated with malignant transformation, evolution and progression of different ovarian cancer subtypes. Tissue from women at risk or who have developed ovarian cancer is interrogated using e.g. next generation sequencing, multiplex immunohistochemistry and spatial profiling to explore the pathogenesis of cancer initiation, evolution and the effects of systemic treatment pressure to identify cell or subtype specific vulnerabilities which may be further exploited in future therapeutic development. Whole genome sequencing of cervical cytology samples is used for the development of a sensitive and specific DNA-based diagnostic assay for early detection of ovarian cancer.

Lethi, Kaisa Professor and Group Leader • Sweden

Moderator

Affiliations: 1) Norwegian University of Science and Technology, Department of Biomedical Laboratory Science 2) Karolinska Institutet, Department of Microbiology, Tumor and Cell Biology.

Research Area: Context-dependent and general mechanisms of tumor invasion, metastasis, and drug resistance with major focus on cell signaling and tumor microenvironment pathways in ovarian cancer. Interest in developing techniques for primary ovarian cancer and stroma cell isolation, ex vivo culture, and biomechanically controlled extracellular matrix models. The group has established ovarian cancer organoids and orthotopic metastasis model and collaborates on different aspects of clinical ovarian cancer therapy development.

Sundfeldt, Karin MD PhD Professor/Consultant • Sweden

Moderator

Ovarian cancer early diagnosis and screening, risk reducing surgery and endometriosis associated ovarian cancer.

Affiliation: Sahlgrenska Academy at Gothenburg University, Sahlgrenska Center for Cancer Research, Dep of Obstetrics and Gynecology and Sahlgrenska University Hospital, Gothenburg.

Research Area: I have a research group at the Institute of Clinical Sciences, Sahlgrenska Academy at Gothenburg University, Sweden. The group specializes in the biology of epithelial ovarian cancer (OC) and our goal is to minimize deaths by detecting OC in curable stages. To accomplish this, we search for new biomarkers for screening and early detection of OC. We have performed several studies with discovery of potential single biomarkers and panels of biomarkers. Blood, ovarian cyst-fluid, cervical and endometrial liquid biopsies is used for discovery and validation studies. Exploring new diagnostic tools for early detection or screening for gynecologic cancer as well as validating promising findings in larger cohorts are just some of the group's current focus areas.

Åvall Lundqvist, Elisabeth M.D., PhD • Sweden

Moderator

Elisabeth Åvall-Lundqvist is a Clinical Gynecologic Oncologist and Professor in Clinical Oncology, at the Department of Clinical and Experimental Medicine, Linköping University in Sweden. She is also Medical Director of the Clinical Trial Unit and Senior consultant at the Department of Oncology, Linköping University Hospital. She is chair of the Swedish Gynecologic Cancer Group.

Research Area: Dr Åvall Lundqvist focus on population-based outcome studies in gynecological cancer. Åvall Lundqvist has been an active PI in phase II-III trials for ovarian cancer trials and served as Director of the Gynecologic Cancer Intergroup as well as President of the Nordic Society of Gynecologic Oncology.

Björkhem-Bergman, Linda MD, PhD, Docent (Assoc Professor) • Sweden

Senior Consultant in Palliative Medicine, Karolinska University Hospital and Docent at Karolinska Institutet.

Associate scientific secretary at the Swedish Cancer Society.

Research area: Palliative medicine with special interest in Vitamin D, immunology and symptom management in palliative cancer care.

Kärre, Klas MD PhD, Professor Emeritus of Molecular Immunology, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm • Sweden

Chairperson, The Scientific Committee of The Swedish Cancer Society

Research Area: Cellular and molecular immunology, NK cells, tumor immunology and immunotherapy.

Zedenius, Jan MD PhD, Professor of Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet • Sweden

Senior Consultant Department of Breast, Endocrine Tumors and Sarcoma, Karolinska University Hospital, Associate Scientific Secretary, the Swedish Cancer Society.

Research area: Prognostic factors in thyroid cancer, adrenal and neuroendocrine tumors.