

**2020-21 Annual Report**  
**Head & Neck Oncology Research**  
**Danny Enepekides, Kevin Higgins, Antoine Eskander**

The Sunnybrook Health Sciences Centre Head and Neck Oncology Division had a productive year with several clinical trials and research projects currently underway.

The division has completed a research project in collaboration with the Department of Dentistry (Dr. Eszter Somogyi-Ganss) and Craniofacial Prosthetics Unit to assess the use, retention, and satisfaction with craniofacial prosthetic devices. The team continues several innovative studies which focus on surgical technique and medical education. Dr. Higgins is the site lead for a multicentre tissue perfusion study which is looking at the assessment of pharyngeal mucosal perfusion status and outcome relative to pharyngocutaneous fistula. He is also the principal investigator on a multicentre thermal imaging assessment of pharyngeal mucosal perfusion status and outcome relative to pharyngocutaneous fistula study which uses novel app-based technology to map out perforators for free flap reconstructions. Both studies are active with prospective data collection. Another prospective research study examining the use and healing rates of Cytal™ Wound Matrix on skin graft donor sites following free-flap procedures is currently in progress. In addition to providing residents and fellows with hands on microsurgical education in the operating room, a novel microsurgical educational model has been designed and is in final development. Future studies will assess its fidelity and use in education.

This year, the department was also very pleased to welcome radiation oncologist Dr. Andrew Bayley to our team who will assist in overseeing several head and neck quality improvement studies. Quality improvement studies at the Odette Cancer Centre are focused on improving time to radiotherapy in the adjuvant setting, staging documentation and accuracy, and after-hours symptom screening/intervention.

A few clinical trials have achieved successful recruitment this year in HPV-associated oropharyngeal SCC; most notably ORATOR II and HN.10 (EVADER), which examine de-escalation radiotherapy vs. trans-oral surgery, and de-escalation radiotherapy, respectively. The Sunnybrook site is an active site and contributor to the upcoming HN.11 study. We will be piloting the injection technique on site as one of the first centres to collaborate with Princess Margaret Hospital on this important study.

Dr. Martin Smoragiewicz, Dr. Antoine Eskander and Dr. Trung Le are leading multicentre clinical trials which will explore the effects of high vs low-dose cisplatin and N-acetyl cysteine (NAC) on ototoxicity for locally advanced head and neck squamous cell carcinomas (HNSCC). Several upcoming trials are assessing the role of novel immunomodulatory agents in combination with immunotherapy and chemotherapy in recurrent/metastatic HNSCC. An active prehabilitation randomized trial is also open for frail patients undergoing head and neck surgery.

Dr. Antoine Eskander was recently awarded the American Association of Otolaryngology – Head & Neck Surgery (AAO-HNS) Health Services Research Grant

and continues his work with his New Investigator Award from the Terry Fox Research Institute and Canadian Institute of Health Research (CIHR). In total Dr. Eskander has received nearly \$1,000,000 in peer-reviewed grant support. Dr. Eskander has also completed his probationary period at ICES as part of the Cancer Program and can now independently complete studies. Dr. Eskander has formal graduate appointment status and is on several thesis committees at the Institute of Health Policy, Management and Evaluation including co-supervision with Dr. Natalie Coburn and one of our own residents, Dr. Christopher Noel, on his PhD thesis.

Many collaborative studies are being completed at Sunnybrook as part of the Canadian Society of Otolaryngology – Head & Neck Surgery (CSO-HNS) Collaborative Research Initiative. These studies include a study assessing locoregional failure in patients with T3 larynx cancer, a study assessing low grade salivary gland cancers and the role of adjuvant radiotherapy, survival outcomes in young patients with oral cavity cancer, and a study assessing the impact of targeted therapy on anaplastic cancer outcomes.

A recent focus has been on COVID-19 and its impact on the cancer system. Several funded studies are underway assessing the impact of the pandemic on cancer surgery, cancer incidence, emergency department use among cancer patients, telehealth use, imaging use, and cancer therapy received (chemotherapy and radiotherapy) as well as wait times. These studies have garnered the research team a lot of media attention including a CTV National News (Avis Favaro) and Globe & Mail (Kelly Grant) feature.

Other active health services research studies at ICES include 1) examining self-harm and psychological distress in cancer patients, 2) examining the impact of anesthesia case volume on outcomes in high-risk cancer surgery, and 3) assessment of patient-centered outcomes in older adults undergoing cancer surgery.

There are three active artificial intelligence and machine learning studies at Sunnybrook. The first assessing a natural language processing algorithm to capture staging data for patients with oropharynx cancer directly from the chart in collaboration with Pentavere. We are also involved in a multicentre study to assess the accuracy of a machine learning algorithm that would pre-screen thyroid cytology slides into a Bethesda classification system. Lastly, we are comparing conventional prediction modeling techniques to machine learning algorithms as it relates to predicting emergency department visits in head and neck cancer patients.

## **2020-21 Annual Report**

### **Head & Neck Surgical Research**

**David Goldstein, Ralph Gilbert, Patrick Gullane, Dale Brown, Jonathan Irish, John de Almeida**

The 2020-2021 academic year has been another productive and successful research year for the Wharton Head and Neck Cancer Surgery research program at the University Health Network. Research at the University Health Network takes place across the three sites, with the majority of research being conducted at the Toronto General Hospital and Princess Margaret Cancer Centre. The two major research programs are the head and neck oncology program and the otology/neurotology program. The head and neck surgical oncology investigators have affiliations with both the Ontario Cancer Institute and the Toronto General Research Institute. The research program is a multidisciplinary program with local, national and international collaborations. Dr. David Goldstein is the director of the head and neck surgical research program at the University Health Network. Members of the UHN head and neck surgical team have several research leadership roles including Dr. John de Almeida as the research lead for the University of Toronto Division of Head and Neck Oncology and Reconstructive Surgery within the Department of Otolaryngology-Head & Neck Surgery and Dr. Jonathan Irish serves as the core lead for the Guided Therapeutics program in the TECHNA Institute, University Health Network.

Over the past academic year the UHN surgeons had over 73 peer reviewed publications, and 7 book chapters published, which is a continued year over year increase. The Robertson Foundation clinical trials program has been established within the UHN head and neck surgical research program. Dr. John de Almeida and Dr. Ali Hosni (head and neck radiation oncologist at the University Health Network) are leading an international trial, the SELECT Trial – SPECT-CT Guided Treatment of the Contralateral Neck in Lateralized Oropharynx Cancer which is also being supported by the Canadian Cooperative Trials Group, as well as by the National Cancer Institute in the United States. The Active Surveillance for low-risk thyroid cancer trial, led by Dr. David Goldstein and Dr. Anna Sawka (Endocrinology, University Health Network), has been expanded out across Canada with recruitment starting at many of the Canadian university centres. The FIND trial-integration of transoral robotic surgery and tailored radiotherapy in the unknown primary cancer setting completed enrolment last year and will be reported early 2022.

Multicentre and co-operative group trials that are in the process of being opened at the UHN include the N-Acetyl Cysteine study to prevent hearing loss in patients undergoing chemoradiotherapy for head and neck cancer led by Dr. Antoine Eskander and Dr. Trung Le at Sunnybrook Health Science Centre (UHN Site Leads: Drs. John de Almeida and John Rutka) an NRG Oncology cooperative group study to evaluate sentinel node biopsy versus neck dissection in early-stage oral cavity cancer (UHN site lead- Dr. Douglas Chepeha). National collaboration in research either as a lead or participating site is being performed in conjunction with the Canadian Society of Otolaryngology-Head & Neck Surgery Collaborative Research Initiative (CRI) Head and Neck Group. There continues to be an ongoing international research collaboration in bioengineering

for head and neck reconstruction, a collaboration between the UHN (Drs. Ralph Gilbert and Jon Irish) and the University of Brescia and University of Padua (Dr. Professor Piero Nicolai). Additional research collaborations in both retrospective and prospective research continued to be fostered with such centres as the Chris O'Brien Life House in Australia, University of Minnesota, University of Alabama, Memorial Sloan Kettering and MD Anderson Cancer Center. The Guided Therapeutics program work and accomplishments are covered in a separate report.

It has also been another outstanding year for grants. Dr. John de Almeida was the recipient of a Canadian Institutes of Health Research Project Grant in the amount of \$3,203,435 for his SELECT trial. Dr. Douglas Chepeha is a co-investigator on this grant. As well, Dr. de Almeida received a Harry Barberian Grant in the amount of \$10,000. Dr. Irish was a co-investigator on a St. Michael's Hospital Foundation Research Investment Council Grant in the amount of \$190,000. Thanks to the generosity of the Shen Family Charitable Foundation, a comprehensive Head and Neck Surgery database is being created that will incorporate data collection into current clinical workflows. Using this approach, patient information will be gathered in real-time from multiple data sources throughout the continuum of care. Implementing this database will help create an all-encompassing clinical research database for Head and Neck oncologic patients that builds on the Anthology of Outcomes Head and Neck Radiation Database. It will also leverage technology to improve clinical workflow while populating clinical database with real time surgical data, outcomes and treatment effects, as well as provide a foundation to help build on our research program in data science and machine learning. Dr. Christopher Yao will soon joining the research program at the UHN as a surgeon investigator whose research focus will be in machine learning and artificial intelligence in head and neck surgery.

Lastly, training and education in research continues to be a priority at the UHN. Our researchers have continued to supervise and train undergraduate students, medical students, residents and fellows in research in otolaryngology-head and neck surgery. Two recent trainee awards at the recent 29th Annual Percy Ireland Academic Day included Best Overall Paper by Hedyeh Ziai (Supervisor: Dr. J. de Almeida) for her work "Machine Learning, Statistical, and National Surgical Quality Improvement Program (NSQIP) Risk Calculators for Predicting Length of Stay After Major Oral Cavity Cancer Surgery" and Best Paper PGY 2 by Adam Kwinter (Supervisor: Dr. D. Goldstein) for his work on "Quantifying Neck Fibrosis and its Quality-of-Life Implications: Development and Validation of the Neck Fibrosis Scale".

## **2020-21 Annual Report**

### **Head & Neck Oncology Research (SH)**

**Ian Witterick, Christina Macmillan, David Fu, Ron Chazen, Anne Hsieh, Jeremy Freeman, Eric Monteiro, Allan Vescan, Lingxin Zhang**

This year continues to be difficult due to the pandemic and access to the lab. We continue to focus on a number of clinical and basic science research projects. Clinical research projects focus on thyroid cancer outcomes. Basic science projects focus on molecular oncology to identify predictive/prognostic molecular signatures, their biological functional roles and signaling pathways that drive thyroid and head & neck cancers.

We use high throughput automated robotic screens to identify novel anti-cancer small molecules/compounds, and characterize their potential therapeutics. Integrating a variety of disciplines, we develop molecular biomarkers at microRNA, mRNA, DNA and/or protein levels through molecular analysis of human cancer tissues or biopsies. We aim to establish early diagnostic assays for identifying pre-cancer patient and prognostic assays for objectively evaluating the patient's overall outcome, and investigate novel therapeutic approaches that transform laboratory discoveries into improving cancer patient care for thyroid cancer and oral cancers.

Current projects this year included developing a molecular assay for detection and quantification of the BRAF mutation in residual tissue from thyroid FNA specimens and investigating Galactin-3 in distinguishing invasive encapsulated carcinoma from noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP).

The recent reclassification of NIFTP raised the need for rebuilding the clinical, histologic, cytological and molecular parameters, including re-evaluation of the previously examined biomarkers, for assisting in the diagnosis of this subset of indolent noninvasive tumors from invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC). In one of our retrospective studies, we have established or refined the diagnostic value of Gal-3 expression as an ancillary marker in identifying NIFTP among encapsulated follicular variant nodules<sup>1</sup>. In addition, the early accurate diagnosis of cancer is still a challenge. Thyroid cancer (90% papillary, PTC) is common, but an estimated 30% of ultrasound-guided fine needle aspirations (FNAs) of thyroid nodules are indeterminate. In our most recent study, we have developed a novel molecular assay to detect BRAF mutation on residual FNA biopsy for definitive diagnosis of malignancy, hence sparing patients from a repeat FNA cytology or diagnostic surgery<sup>2</sup>.

1. Fu G., Polyakova O, Chazen RS, Freeman J, Witterick I. Diagnostic value of Galectin-3 in distinguishing invasive encapsulated carcinoma from noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP). *Cancers* 2021,13(12), 2988.

2. Fu G., Chazen R.S., MacMillan C., Witterick I. Development of a molecular assay for detection and quantification of the BRAF mutation in residual tissue from thyroid nodule fine-needle aspiration biopsy specimens. *JAMA Network Open* 2021, 1;4(10).

**2020-21 Annual Report**  
**Head & Neck Translational Program**  
**Fei-Fei Liu**

The Head and Neck Cancer (HNC) Translational Research Program at the Princess Margaret strives for a future where HNC can be cured without toxicity. This program has three main goals: 1) To understand HNC biology at the molecular, cellular, and tumour levels; 2) To elucidate the molecular and genetic bases of treatment toxicities in response to radiation, with or without chemotherapy; and, 3) To train young scientists and physicians in the scientific pursuits of understanding HNC. Our research team comprises of over 80 clinicians, scientists and research personnel, collectively working on several projects, including: tumour initiating cells, genetic determinants of outcome, biomarkers & novel drug discovery, proteomic studies, treatment of human papilloma virus (HPV) associated oropharynx cancer, and prognostic value of imaging-omic data.

Each year, our team publishes over 100 peer-reviewed publications in leading scientific journals. This year has seen numerous advances in HNC research. First, I would like to congratulate the clinical trials teams at the Princess Margaret Cancer Centre (PM) - University Health Network (UHN). Based on accrual updates shared at the 2021 NRG Oncology semi-annual virtual meeting for January to June 2021, the site accruals at the PM-UHN for NRG clinical trials are number one in Canada, number two in Non-US sites, and number four in Global Main Member Sites! In particular, two HNC trials (NRG-HN007 and NRG-HN004) are among the top accruing clinical studies at the PM.

Secondly, Dr. Scott Bratman has been appointed as the Dr. Mariano Antonio Elia Chair in Head and Neck Cancer Research for a 5-year term, effective December 1, 2020. The Dr. Mariano Antonio Elia Chair was established in 2001 with the vision to create a future of personalized HNC therapy with no toxicity. Since his arrival at the Princess Margaret in 2014, Dr. Bratman has rapidly established himself as an internationally recognized expert in liquid biopsy, HNC, and personalized radiation medicine. His research program encompasses HNC-focused clinical and translational studies, with the overarching goal of developing biomarkers for improved diagnosis and treatment of HNC. In this role, Dr. Bratman aims to advance HNC research on multiple fronts, both in his laboratory and in partnership with clinical colleagues, data scientists, clinical trial groups, as well as industry.

Finally, a research team led by Dr. John Waldron and Ms. Sophie Huang published a study in *Cancer*, which confirmed the clinical utility of hypofractionated radiotherapy (RT-hypo) in subsets of head and neck squamous cell carcinoma (HNSCC) patients receiving treatment during the COVID-19 pandemic. The authors proposed that delivery of RT-hypo in place of concurrent chemoradiotherapy could reduce hospital visits and bypass immunosuppressive effects of chemotherapy to decrease risk of COVID-19 infection.