

Head and Neck Oncology

Head & Neck Oncology Research (SHSC)

Danny Enepekides, Kevin Higgins, Antoine Eskander

INSPIRE Trial

Randomized Phase II Trial of Neoadjuvant and Adjuvant Therapy with the IRX-2 Regimen in Patients with Newly Diagnosed Stage II, III or IVA Squamous Cell Carcinoma of the Oral Cavity.

The objectives of this phase 2 study are to determine if event-free survival (EFS) of subjects treated with the IRX-2 regimen is longer than for subjects treated with Regimen 2 and to compare the safety and feasibility of each regimen. Accrual opened in May 2017. Project is ongoing/active.

ORATOR 2

A Phase II Randomized Trial of Treatment De-Escalation for HPV-Associated Oropharyngeal Squamous Cell Carcinoma: Radiotherapy vs. Trans-Oral Surgery (ORATOR II).

The purpose of this phase 2 study is to compare progression free survival relative to historical controls for de-intensified primary radiotherapy versus transoral surgery and neck dissection with or without adjuvant radiotherapy in patients with early T-stage, HPV-positive squamous cell carcinoma of the oropharynx, and to compare toxicity and quality of life (QOL) profiles. Project is ongoing/active.

ACS NSQIP Risk Calculator

Predicting Complications of Major Head and Neck Oncological Surgery: An Evaluation of the ACS NSQIP Surgical Risk Calculator.

The aim of this study is to provide the first comprehensive evaluation of the ACS NSQIP surgical risk calculator for head and neck surgery in a Canadian setting. This manuscript was successfully

published in Journal of Otolaryngology Head & Neck Surgery in March 2018. Project is complete.
<https://www.ncbi.nlm.nih.gov/pubmed/?term=Predicting+complications+of+major+head+and+neck+oncological+surgery%3A+an+evaluation+of+the+ACS+NSQIP+surgical+risk+calculator>.

Anterolateral Thigh (ALT) Perforator Free Flap

Motor and Sensory Morbidity Associated with the Anterolateral Thigh Perforator Free Flap: A Pilot Study.

The objective of this study is to quantify changes in motor function, sensation, and lower extremity quality of life following anterior lateral thigh free flap (ALT) resection. This study was accepted for publication in The Laryngoscope in June 2017. Project is complete.

<https://www.ncbi.nlm.nih.gov/pubmed/29105774>

Low Risk Papillary Thyroid Cancer

A Protocol for a Canadian Prospective Observational Study of Decision-Making on Active Surveillance or Surgery for Low-risk Papillary Thyroid Cancer.

This is a multiphase prospective observational study. The goal of phase 1 was to determine the percentage of VL-PTC patients who chose AS over surgery and the reasons for their treatment choice. Phase 2 evaluated decision regret at one year in VL-PTC patients who completed phase 1 and either underwent AS or surgery. The manuscript was successfully published in BMJ Open in April 2018. Project is complete.

<https://www.ncbi.nlm.nih.gov/pubmed/29654030>

Web-based Tool for Thyroidectomy

A Web-Based Tool to Improve Perioperative Patient Experience for Patients Undergoing Thyroidectomy.

This study serves to assess the impact of an instructional website tool on the satisfaction and comprehension of patients undergoing thyroidectomy. Project is ongoing.

Fistula

Association of Pharyngocutaneous Fistula on Locoregional Control in Laryngectomy Patients: A Multi-Institutional Collaborative study.

The main objective of this study is to determine if pharyngocutaneous fistula following total laryngectomy is associated with an alteration in locoregional control and distant metastasis. This study is a multi-institutional collaboration between Memorial Sloan Kettering, MD Anderson, University of Alberta, Sunnybrook and the University Health Network. Project is ongoing.

G-Tube

Incidence of Stoma Site Metastases in the Push Vs. Pull Technique for Percutaneous Endoscopic Gastrostomy (PEG) Tube Placement in Head and Neck Cancer.

The purpose of this study is to compare the incidence of stoma metastases between the push and pull techniques for head and neck cancer patients who underwent a perioperative PEG insertion at Sunnybrook Health Sciences Centre and Ohio State University. Project is ongoing/active.

Radiomics

Establishing a Radiomics Signature to Predict Residual Malignancy in All Head and Neck Cancers.

The primary objective of the study is to create a unique and validated radiomics signature for persistent lymphadenopathy in patients with HPV+ OPSCC treated with primary radiation or chemoradiation with curative intent. This study is a multi-institutional collaboration between Sunnybrook Health Science Centre, Princess Margaret Cancer Centre and University Health Network. Project is ongoing/active.

Hypopharynx

The Role of Collagen Markers Upon Outcomes of Hypopharyngeal Cancer - A Retrospective Study.

This study is run in collaboration with research teams in the United Kingdom and University Health Network. The primary purpose is to develop the largest database of hypopharyngeal cancer in the medical literature to date. From this, a database of tissue from included patients will be built to compare the presence of tissue biomarkers with patient survival outcomes. In addition, an idea of the natural presentation and history of the condition will be studied. Project is ongoing/active.

SPY

Intraoperative Evaluation of Pharyngeal Mucosa and Cervical Skin Utilizing SPY Fluorescence Angiography to Prevent Wound Complications, A Retrospective Review.

This study aims to evaluate Laser assisted fluorescent dye in assessing post-laryngectomy pharyngeal mucosa and regional/free flap perfusion in head and neck cancer surgery/reconstruction and correlate with rates of postoperative wound complications. Project is ongoing/active.

Perineural Invasion of Squamous Cell Carcinoma Tubular Neck Mass

This case report documents the diagnosis and treatment of a patient that developed extensive perineural and intraneural invasion along the Greater Auricular Nerve (GAN), from lobule to Erb's point. In addition, it provides a review of the literature on intraneural spread of head and neck malignancies. The manuscript was successfully published in JAMA Otolaryngology in May 2018. Project is complete. <https://www.ncbi.nlm.nih.gov/pubmed/29596558>

Thyroid disorders in the Elderly:

An Overall Summary

The purpose of this article is to shed light on the distinct difference in medical care of the elderly from that of younger counterparts and to address inherent

complexities in caring for elderly patients in an effort to improve quality of care. Topics considered range from general anatomic challenges to underlying biochemistry to adjuvant therapy options and surveillance. Published in *Clinics of Geriatric Medicine* in May 2018. Project is complete.
<https://www.ncbi.nlm.nih.gov/pubmed/29661337>

Geriatric Free Tissue Transfer

Determining Relative Diagnostic Efficacy of Ultrasound Follow-Up in Advanced Neck Diseases Patients.

We aim to evaluate the use of US as a diagnostic tool for follow-up in head and neck patients at a quaternary Canadian care centre. Specifically, we intend to delineate the period until detection, accuracy in detecting involved nodes, and long-term outcomes for these patients compared to patients that did not undergo regular US imaging. Project is ongoing.

Supraclavicular Island Flap and Submental Flap

Use of Supraclavicular Artery Island Flap and Submental Artery Island Flap for Head and Neck Reconstructions: An Illustrative Case Series.

The purpose of this study is to document the experiences of using the SCAIF and SMAF at a major Canadian quaternary care centre. Special focus will be paid to surgical technique, indications, and flap modifications. Illustrations will be incorporated to detail the procedure process. Project is ongoing.

Ultrasound Follow-up

Determining Relative Diagnostic Efficacy of Ultrasound Follow up in Advanced Neck Diseases.

We aim to evaluate the use of ultrasound as a diagnostic tool for follow-up in head and neck patients at a quaternary Canadian care centre. Specifically, we intend to delineate the period until detection, accuracy in detecting involved nodes, and long-term outcomes for these patients compared to patients that did not undergo regular US imaging. Project is ongoing.

Venous Thromboembolism

Systematic Review and Meta-analysis of Venous Thromboembolism in Otolaryngology-Head and Neck Surgery

The purpose of this study was to present our systematic review and meta-analysis of the data on venous thromboembolism (VTE; deep venous thrombosis [DVT] and/or pulmonary embolism [PE]) in otolaryngology-head and neck surgery (OHNS). Published in *Head & Neck* in March 2017.
<https://www.ncbi.nlm.nih.gov/pubmed/28370756>

Laryngeal and Hypopharyngeal Cancer

Overview of Surgery for Laryngeal and Hypopharyngeal Cancer in Ontario, 2003-2010.

The primary purpose of this study was to describe variations in incidence rates, resections rates, and types of surgical resection for patients diagnosed with laryngeal and hypopharyngeal cancers in Ontario. Published in *Head & Neck* in June 2017.
<https://www.ncbi.nlm.nih.gov/pubmed/?term=Overview+of+surgery+for+laryngeal+and+hypopharyngeal+cancer+in+Ontario%2C+2003-2010>.

HPV-positive Oropharyngeal Cancer

Appraisal of the AJCC 8th Edition Pathologic Staging Modifications for HPV-positive Oropharyngeal Cancer, a Study of the National Cancer Database.

The purpose of this study was to validate the American Joint Commission on Cancer's new staging system for human papillomavirus associated oropharyngeal cancer using the National Cancer Database. Published in *Oral Oncology* Vol 73 in September 2017.
<https://www.ncbi.nlm.nih.gov/pubmed/?term=Appraisal+of+the+AJCC+8th+edition+pathologic+staging+modifications+for+HPV-positive+oropharyngeal+cancer%2C+a+study+of+the+National+Cancer+Data+Base>

AHNS Series

AHNS Series: Do you know your guidelines? Guideline Recommendations for Head and Neck Cancer of Unknown Primary Site.

The primary purpose of this series is to raise awareness of the current guidelines in head and neck oncology by reviewing the recommendations and the evidence supporting such recommendations, particularly those published by the National Comprehensive Cancer Network (NCCN). Published in *Head & Neck* in November 2017. <https://www.ncbi.nlm.nih.gov/pubmed/?term=AHNS+Series%3A+Do+you+know+your+guidelines%3F+Guideline+recommendations+for+head+and+neck+cancer+of+unknown+primary+site>.

Free Flap Reconstruction

Predictors of Complications in Patients Receiving Head and Neck Free Flap Reconstructive Procedures.

The study objectives are to determine the overall complication rate, wound healing, and wound infection complications and identify preoperative, intraoperative, and postoperative predictors of these complications. Published in *Otolaryngology Head and Neck Surgery* in April 2018. <https://www.ncbi.nlm.nih.gov/pubmed/?term=Predictors+of+Complications+in+Patients+Receiving+Head+and+Neck+Free+Flap+Reconstructive+Procedures>.

Choosing Wisely Campaign

Head and Neck Surgical Oncology Choosing Wisely Campaign: imaging for patients with hoarseness, fine needle aspiration for neck mass, and ultrasound for odynophagia.

Choosing Wisely Canada is a campaign designed to raise awareness regarding inappropriate or unnecessary tests and treatments. The Canadian Society of Otolaryngology - Head & Neck Surgery and the Canadian Association of Head and Neck Surgical Oncologists developed a Choosing Wisely Canada list to help promote high quality care for patients presenting with disorders of the head and neck. Published in *Otolaryngology Head and Neck*

Surgery in January 2018.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Head+and+Neck+Surgical+Oncology+Choosing+Wisely+Campaign%3A+imaging+for+patients+with+hoarseness%2C+fine+needle+aspiration+for+neck+mass%2C+and+ultrasound+for+odynophagia>.

Subscapular System of Flaps

Supine Positioning for the Subscapular System of Flaps: A Pictorial Essay.

This pictorial essay demonstrates a modification to the positioning, prepping, and draping technique for the subscapular system of flaps allowing the patient to be placed supine and without the need for a second assistant during the harvest or closure. Published in *Head & Neck* in February 2018. <https://www.ncbi.nlm.nih.gov/pubmed/?term=Supine+positioning+for+the+subscapular+system+of+flaps%3A+A+pictorial+essay>

Statistically Significant Randomized Trials

The Fragility of Statistically Significant Findings from Randomized Trials in Head and Neck Surgery.

We sought to calculate the Fragility Index scores for randomized control trials in the head and neck cancer literature where surgery was a primary intervention. Published in *The Laryngoscope* in April 2018.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=The+fragility+of+statistically+significant+findings+from+randomized+trials+in+head+and+neck+surgery>

Considerations for Head and Neck Surgery

Surgical Considerations in Advance Basal Cell Carcinoma, Cutaneous Squamous Cell Carcinoma, and Cutaneous Melanoma: A Head and Neck Perspective.

In this review, we aim to discuss the appropriate surgical management of skin cancers and associated controversies as it pertains to the head and neck. Published in *Current Otorhinolaryngology Reports* in June 2018.

<https://link.springer.com/article/10.1007/s40136-018-0195-3>

Lateral Arm Free Flap

The Unique and Valuable Soft Tissue Free Flap in Head and Neck Reconstruction: Lateral arm.

In this publication a detailed anatomic and harvest technique is described for the lateral arm free flap, along with indications and advantages of its use for head and neck reconstruction. A scoping literature review was also conducted to tabulate indications, overall success and complications of the flap.

Published in Oral Oncology in May 2018.

<https://www.ncbi.nlm.nih.gov/pubmed/29909883>

Grant Applications

Dr. Antoine Eskander

Thyroid Surgery Quality of Care in Ontario: Impact of Cancer Care Ontario's Quality-Based Procedure (QBP) Program. Harry Barberian Scholarship Fund. [\$7,500 CAD].

Collaborators: Eric Monteiro, Jesse Pasternak, David Goldstein, Jonathan Irish. PI- Dr. Antoine Eskander. Timeline: 2018 April – 2019 March.

Head & Neck Surgical Research (UHN)

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

The 2017–2018 academic year has been another productive 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 occurring between the Toronto General Hospital and Princess Margaret Cancer Centre. The surgeon investigators for the head and neck oncology program 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. The research program has 4 major themes: 1. Guided therapeutics program whose work is covered in a separate report. 2. Clinical outcomes research in head and neck oncology and reconstructive surgery.

Outcomes research includes clinical trials and prospective and retrospective observational studies in mucosal, salivary gland, endocrine and skull base neoplasms. In addition, there is a major focus on evaluation of outcomes with microsurgical reconstruction and functional outcomes including quality of life assessment. 3. Basic science and translational research program is a multidisciplinary program that involves radiation and medical oncology, pathology, and basic science labs. Research includes proteomics, genomics, stem cell research, and molecular epidemiology. A large focus of the program is on the identification and assessment of biomarkers in the treatment of head and neck cancer. 4. Health services research with a focus on quality of care and cost-effectiveness. Resident and fellow research is a major component of the research program. There have been a number of residents and fellows who have been mentored and supported by members of the head and neck surgery research program.

In the 2017–2018 academic year the UHN surgeons had over 49 peer-reviewed publications accepted or in-press, \$6,832,463 secured in new grant funding including a \$6,616,301 Terry Fox New Frontiers Program Project Grant on porphyrin-enabled image-guided cancer interventions lead by Dr. Jon Irish and Dr. Gang Zheng. Dr. Caitlin McMullen's project, supervised by Dr. John de Almeida, on occult nodal disease and occult extranodal extension in oropharyngeal SCC in patients undergoing TORS won the Robert Byers Award for best clinical paper at the 2018 American Head and Neck Society meeting. Current ongoing novel prospective clinical research studies include the FIND trial (role of transoral robotic surgery in the unknown primary squamous cancer of the head and neck), quality of life comparison between open vs endoscopic skull base surgery, active surveillance for low risk thyroid cancer, oral biofeedback trial for patients with oral cavity cancer, assessment of speech and swallowing in patients with treatment for upper aerodigestive tract cancers, and mapping of head and neck utilities in head and neck cancer patients. Dr. Irish continues to lead numerous pre-clinical and clinical studies through the Guided therapeutics program which is reported separately. Dr. Chepeha

has developed a multi-level research database, called Intrepid, and is currently working with Techna to incorporate prospective research seamlessly into clinical work flow.

The Head and Neck Cancer Translational Research Program continues to enroll patients prospectively collecting blood, tissue and information on out-of-pocket costs, frailty, risk factor behaviours, utilities, and speech and swallowing. The surgical program continues to build on its radiomics program through collaborations with radiation oncology and bioinformatics.

Head & Neck Oncology Research (SHS)

Ian Witterick, Paul Walfish, Christina Macmillan, David Fu, Ron Chazen, Anne Hsieh, Jeremy Freeman, Eric Monteiro, Allan Vescan, John de Almeida.

Research interest:

We focus on conducting patient-oriented translational molecular oncology to identify predictive/prognostic molecular signatures, their biological functional roles and signaling pathways that drive thyroid and head & neck cancers. Using high throughput automated robotic screens, we 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 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 head & neck cancers.

Research directions:

1. Characterize novel anti-cancer molecules and cancer therapeutics;
2. Identify molecular biomarkers for developing diagnostic and prognostic methods for thyroid carcinoma and head & neck cancers

Objectives: Understanding genomic and proteomic characteristics underlying cancer development. Discovering novel predictive markers to detect cancers earlier, when cure rates are highest, and novel prognostic markers to evaluate patient survival; and developing effective therapy strategy using molecular testing of patient response to drug treatment.

1. Establishing the informative clinical database for head & neck and thyroid cancers. Database integrating molecular, histopathological and clinical information greatly expands our understanding of the molecular basis of tumor progression and helps develop prognostic and predictive markers with specific clinical contexts.
2. Investigating molecular genetics, their biological functional roles in oral and thyroid cancer with the goal of discovering novel anti-cancer molecules to improve cancer therapies. We want to gain a better understanding of how clinic genomic and proteomic characteristics work together to affect oral or thyroid cancer progression and prognosis.
3. Identifying gene signatures and developing molecular biomarker based methods for cancer diagnoses and prognoses with small amounts of FFPE tumor material, fine needle aspiration (FNA) biopsy, circulating tumor cells or patient blood samples.
4. On-site laboratory molecular testing of patient tumors to assist cancer risk diagnosis and the selection of patients for treatment, and to develop treatment strategies for precise medicine therapies of head & neck and thyroid cancers.
5. International collaboration for clinical oncology. Interpretation of clinic impact will require a coordinated effort from different clinical laboratories/hospitals across the community for patient cohort sharing, analyzing and curating data to advance genomic medicine.

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 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. In the first half of 2018, Dr. Fei-Fei Liu's group had already published two studies in *Oncogenesis* and *Int J Radiat Oncol Biol Phys*. The first study by Bissey et al. revealed a novel mechanism of chemoresistance in nasopharyngeal carcinoma (NPC) via miR-449b, an overexpressed gene from the group's previously validated 4-microRNA signature predictive of distant metastasis risk in NPC. The second study by Kwan et al. demonstrated that radiomic biomarkers improve the risk stratification of distant metastasis in patients with non-metastatic human papillomavirus (HPV)-related oropharyngeal cancers (OPCs). Used alone or in conjunction with other clinical factors, these radiomic biomarkers will allow for greater precision when assigning systemic therapy for non-metastatic HPV-related OPC.

Furthermore, Dr. Liu was the co-chair of the 2018 Gordon Research Conference for NPC, "New Perspectives on the Virus-Host Interplay in Nasopharyngeal Carcinoma and Their Impact on Diagnosis and Therapeutic Interventions" held in Hong Kong. The conference highlighted many

recent advances in various fields of NPC, ranging from Epstein-Barr virus (EBV) infection in pathogenesis, elucidation of the genetic landscape and signaling pathways, advances in detection and diagnosis, plus novel therapeutic approaches. The conference was a massive success, and provided an open forum for internationally renowned clinicians and scientists to exchange and brainstorm on cutting-edge research, identify challenges in therapy, and formulate innovative strategies against NPC.