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1. ASSESSING CASCADE CARRIER TESTING FOR HEREDITARY BREAST AND OVARIAN CANCER

Bedard V.K.*, Bedard A.C.*, Nuk J., Bedard J.R.J., Sun S., SCHRAIDER K.A.

*co-first authorship

Category: Population Health/Health Services

Introduction: Cascade carrier testing for hereditary cancer enables identification of at-risk individuals most likely to benefit from increased screening and preventative measures. Despite predicted positive health outcomes, there is a paucity of recent literature on the uptake and health impact of program-wide carrier testing for hereditary cancer.

Methodology: We assessed carrier testing uptake and demographic factors between January 1, 1997 and December 31, 2016 for families in which the index patient received testing through the Hereditary Cancer Program (HCP) in British Columbia, Canada. We began with BRCA1 and BRCA2 and will be conducting additional analyses on other high and moderate penetrance genes tested by the HCP. Future analyses will elucidate the health impact of carrier testing for hereditary breast and ovarian cancer syndrome.

Results: A total of 424 and 398 positive BRCA1 and BRCA2 index cases, respectively, have been identified through our provincial program; carrier testing for at-risk family members has been performed for 723 and 664 individuals for BRCA1 and BRCA2, respectively. 45% (323/723) tested positive for a BRCA1 mutation and 45% tested positive for a mutation in BRCA2 (298/664). The average age of individuals receiving carrier testing for BRCA1 was 46.0 ± 15.9 years, and 47.7 ± 16.3 years for BRCA2. There was a significantly higher number of females (n=1051) than males (n=336) receiving carrier testing for BRCA1 and BRCA2 (p < 0.01). In families with pathogenic or likely pathogenic mutations in BRCA1 and BRCA2, a mean of 1.7 carrier tests per index test was performed. Carrier testing uptake corresponded with the geographic population distribution of the province.

Conclusion: This analysis highlights the carrier testing uptake for BRCA1 and BRCA2 mutations in the population served by the HCP. Future analyses may inform decisions regarding how resources may be allocated to better serve this high-risk population.
2. DNA-DIRECT: INCREASING EFFICIENCY FOR PRE-TEST GENETIC COUNSELING IN MULTI-GENE PANEL TESTING

Bedard A.C., Nuk J.E., Lawrence C., Sun S., SCHRADER K.A.

Category: Population Health/Health Services

Introduction: With increasing demand for cancer genetics services, alternate modes of service delivery are being considered. One alternative is termed DNA-direct, which was studied and successfully implemented with BRCA1 and BRCA2 testing in the Netherlands. DNA-direct delivers an abbreviated pre-test telephone appointment to expedite the testing process. In April 2017, the Hereditary Cancer Program of BC Cancer, Canada began trialing DNA-direct for patients undergoing multi-gene panel testing.

Methodology: The process included: 1) triage of eligible patients (geographic location, fluency in English, eligibility for index testing); 2) brief telephone appointment to review the reason for referral, an abbreviated psychosocial assessment, and review of the testing process; and 3) mailing a package containing testing forms and written educational materials. Once results were received, patients were scheduled for a typical results disclosure appointment. Patients consenting to further contact were sent the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire, assessing for coping and adaptation to genetic test results, and scores were compared with patients seen with a traditional pre-test appointment.

Results: Over a 7-month period 112 patients had a DNA-direct appointment. There was a greater than 95% acceptance rate for the appointment type. The average time spent for the pre-test telephone appointment was 15 minutes. The majority of patients were referred for query hereditary breast and ovarian cancer syndrome (82%). Of the 62 results returned to date, 8 pathogenic mutations were detected. The results of the MICRA have shown no statistically significant difference between patients who had a DNA-direct versus a longer traditional pre-test appointment (n = 117).

Conclusion: The DNA-direct approach demonstrates significant efficiencies in pre-test genetic testing appointments. Patient satisfaction and distress levels are comparable to those served with longer pre-test appointments. DNA-direct is efficacious in the setting of multi-gene panel testing and helps to address increasing demands for service.
3. GENETIC CARRIER TESTING FOR HEREDITARY CANCER IN BRITISH COLUMBIA
AND YUKON: AN OVERVIEW OF THE PAST 20 YEARS

Braley E., Bedard A., Beard V., Asrat M.-J., Aubertin G., Binnington K., Cremin C., Compton K.,
Creighton S., Lohn Z., Heidary N., Kaurah P., McCullum M., Mindlin A., Nuk J., O’Loughlin M.,
Petersen T., Portigal-Todd C., Scott J., St-Martin G., Thomas R., Thompson J., Bedard J.,
Schrader K., SUN S.

Category: Population Health/Health Services

Introduction: Genetic carrier testing for hereditary cancer is a highly accurate and cost-
effective method for identifying individuals at high risk for cancer, who will significantly benefit
from increased screening and/or prevention methods. BC Cancer’s Hereditary Cancer Program
has provided the vast majority of the cancer genetic counselling service for the population of
British Columbia and the Yukon for the past 22 years. This study is a descriptive analysis of
genetic carrier testing facilitated by the program in its first 20 years of operation.

Methods: The HCP’s program database was queried for all carrier tests facilitated between
January 1, 1997 and December 31, 2016. The compiled dataset consisted of variables including
gender, age, postal code, referral source, genes tested, and cancer diagnoses. Descriptive
statistics were computed; mean and standard deviation is reported for continuous variables and
proportion is reported for categorical variables.

Results: This analysis revealed that 3605 individuals, from 1709 families, have had carrier
testing with our program over the past 20 years; 47 individuals received greater than one carrier
test. 55% of test results were positive and 45% of results were negative. Demographic analysis
showed 72% of those tested were female and 28% were male; and 84% of tests were for
individuals living in urban areas compared to 13% of tests were for those living in a rural area,
which is in keeping with BC Census data. The mean age of individuals seeking carrier testing
was 46.6 (SD = 17). The majority of carrier tests were for BRCA1 and BRCA2 (68%), followed
by 17% for Lynch Syndrome, and 15% for other genes. The proportion of referrals for
appointments from family doctors (33%) was close to that from self-referrals (37%).
Furthermore, carrier testing has steadily increased over time, with 83% of tests completed in the
second decade. Cancer diagnoses for individuals who received carrier testing will be analyzed,
including a comparison of the timing of the diagnoses versus the timing of the genetic test
results.

Discussion: Significantly more females than males have received carrier testing for hereditary
cancer syndromes, highlighting the need to research what is normative health seeking behavior
for males and potential barriers to testing for them. We also found that the average age of
testing is 46, which is considerably older than the age by which most hereditary cancer
screening protocols begin, demonstrating another area of opportunity. By deepening our
understanding of the program’s experience in its first 20 years, we are able to identify potential
gaps in service, inspire new avenues for exploration, and serve as a benchmark for new
initiatives going forward.
4. MICROFLUIDICS: AN EFFECTIVE TOOL IN MODULATING THE PHYSICAL PARAMETERS OF PROTEIN NANOPARTICLES FOR CANCER THERAPY

VAN BALLEGOOIE C.1,5, Andreu I.2,5, Pallaoro A.2,5, Gates B.2, Bally M.3-5, Yapp D.3,5

1University of British Columbia Faculty of Medicine; 2Simon Fraser University Faculty of Chemistry; 3University of British Columbia Faculty of Pharmaceutical Sciences; 4University of British Columbia Faculty of Pathology and Laboratory Medicine; 5British Columbia Cancer Research Centre

Category: Biology/Informatics

As the number of nanoparticle-based drugs increases, the role of the manufacturing process becomes a critical factor in determining the drug’s success in terms of the scalability of the system and reproducibility of the products. The reproducibility of particles under 100 nm using conventional methods, such as emulsion solvent diffusion and emulsion solvent evaporation, is often unreliable in replicating the same size and polydispersity between batch-to-batch syntheses [1]. Additionally, the ability to easily modulate the system in order to fine tune the nanoparticle’s (NP) size is a desirable attribute when considering the synthesis methods as size plays a critical role in tissue penetration and cellular uptake, biodistribution, drug release kinetics and drug efficacy [2]. One method to achieve a reproducible, tunable system is through the use of microfluidics [3]. Parameters such as the total flow rate of the fluidics system, relative flow rate of the aqueous phase and organic phase within the fluidics system, the concentration of the base material, the concentration of the solvent, and the properties of the solvent can influence the polydispersity and diameter of the NPs when utilizing a microfluidics system. These conditions were assessed using a commercially available Y-junction microfluidics chip with staggered herringbone micromixers. Herein, we examine the size and polydispersity of a protein-based NP, Zein, under varying conditions using microfluidics and evaluate its potential as a NP carrier for cancer therapy.


**Figure 1:** Precipitation method used to form Zein nanoparticles as a drug delivery platform

**Figure 2:** Simplified method of synthesizing and analyzing Zein nanoparticles produced using microfluidics
6. LOSS OF FBXO11 FUNCTIONS CONTRIBUTES TO ACUTE MYELOID LEUKEMIA

Mo A. (Trainee), Chang L., Duns G., Ibrahim R., Docking R., Umlandt P., Parker J., KARSAN A.

TFRI Program Title: The Terry Fox New Frontiers Program Project Grant in Exploiting Pathogenic Mechanisms in Acute Leukemia for Clinical Translation (TFRI Program Project Grant number 1074)

TFRI Research Project Title: Disruption of the Ubiquitin-Proteasome System in AML

Category: Biology/Informatics

Acute myeloid leukemia (AML) is the most common adult leukemia (~80% of cases), and AML patients have poor prognosis, with a 5 year survival rate of about 28%. However, there has been little advancement in therapeutic options for AML patients in the last couple decades. The ubiquitin proteasome system (UPS) plays important roles in regulating a range of essential cell functions and has been shown to be dysregulated in various cancer types. We identified somatic mutations in UPS genes in 11.4% of AML cases from next generation sequencing data of 140 clinical AML samples, as well as in 10.7% of cases from the TCGA AML dataset.

Heterozygous inactivation of FBXO11, which codes the substrate-recognizing component of the SKP1-CUL1-F-BOX (SCF) ubiquitin E3-ligase complex, by truncating mutations or copy number loss was found in 3/38 patients with UPS mutations. Additionally, on average, AML patients have reduced FBXO11 transcript expression compared to normal cells. In a mouse bone marrow transplant experiment, we found that knockdown of Fbxo11 by short-hairpin RNA (shRNA) cooperates with the expression of the AML1-ETO fusion protein to drive leukemia development. We observed an expansion in the phenotypic hematopoietic stem cell population in the leukemic mouse bone marrow. We also found the leukemia to be transplantable into secondary recipients. This suggests the presence of leukemic stem cells in the bone marrow, which are capable of initiating hematopoietic malignancy. Leukemic stem cells tend to be quiescent and thus more chemoresistant. Knockdown of FBXO11 by shRNAs in CD34+ normal human hematopoietic progenitor cells results in increased maintenance of a stem/progenitor phenotype, and reduced erythroid differentiation.

To identify SCF-FBXO11 ubiquitination targets that are contributing to the outcomes of FBXO11 loss through dysregulated protein expression, we performed mass spectrometry analyses of protein lysate from FBXO11 CRISPR/Cas9 knockout myeloid K562 cells, co-immunoprecipitated with FLAG-FBXO11, or with the di-Glycine peptide remnant from ubiquitin trypsinolysis. The results suggest SCF-FBXO11 regulates the expression of proteins involved in regulating oxidative phosphorylation and buffering oxidative stress.

These results suggest that FBXO11 plays a role in regulating stem/progenitor cell maintenance in both normal and leukemic conditions. SCF-FBXO11 acts as a tumor suppressor in AML, highlighting the importance of UPS deregulation in cancer development. Considering the prevalence of FBXO11 loss in AML patients, understanding the mechanisms of its role in leukemogenesis could lead to the identification of new therapeutic targets.
Background: Through media, Internet, and supportive community programs, patients are able to share cancer-related experiences. It can be difficult for patients to assess if the information about radiation that they encounter is accurate and relevant to one's own situation. In order for physicians to recognize patients’ concerns and help them make decisions about breast radiotherapy (BRT), a better understanding of how patients are educating themselves and the types of information they have encountered is valuable.

Objective: The purpose of this study is to assess breast cancer patients' information-seeking behaviours, needs and perceptions of BRT prior to radiation oncology consultation.

Methods: Breast cancer patients referred for adjuvant BRT at BC Cancer, > 18 years, without a history of prior BRT, were asked to complete an anonymous survey prior to their radiation oncology consultation. Likert scale, multiple choice and open-ended questions were used to assess information sources, knowledge, and perceptions of BRT.

Results: The response rate was 86%; 118/137 patients approached agreed to participate in the study. Most patients were >50 years old (66%) and 60% had a post-secondary degree or diploma. The most commonly reported sources of information about BRT were healthcare providers (HCP, 55%), family or friends treated with BRT (53%), and the Internet (45%). Patients indicated that these sources were also most trustworthy or reliable. Few received information about BRT from traditional media (13%), scientific articles (12%), social media (5%), and support groups (3%). Most patients reported having little or no knowledge about BRT (79%). Most (67%) were a little or moderately concerned about the side effects of BRT, while 29% were very concerned. Half were unsure about the benefit of BRT and 46% thought BRT would provide a moderate to significant benefit. While educating themselves about BRT, a wide range of topics were encountered, and the most common ones were fatigue (68%), skin care (57%) skin problems (54%), effects on healthy body tissues (43%), effects on the immune system (37%), and pain (34%). Several other topics were encountered, including BRT and bone health (32%), second cancers (32%), problems with heart (31%), lungs (30%), arm swelling (27%), recommended activity during BRT (27%), GI side effects (26%), dietary recommendations (24%), radioactivity (19%), and hair loss (19%). Of these topics encountered, those patients considered the most important for the radiation oncologist to address were BRT effects on the heart (74%), second cancers (74%), immune system (66%), and pain (64%). Although commonly encountered topics, relatively fewer patients indicated fatigue (56%) and skin care (49%) as important issues to be addressed at their consultation.

Conclusion: Breast cancer patients encounter a broad range of information about BRT from a variety of sources prior to their radiation oncology consultation and many are concerned about the potential side effects. Patients surveyed felt that rare and serious side effects were the most important for radiation oncologists to address during consultation.
8. LOCAL RELAPSE AND SURVIVAL OUTCOMES IN PATIENTS WITH SCALP SARCOMA

Jasper K. (PGY-3), HOLLOWAY C., DeVries K., Truong P.

BC Cancer and University of British Columbia

Category: Translational/Clinical

Purpose: There is limited literature on the optimal treatment of sarcoma arising in the scalp. This study evaluates local relapse and survival outcomes of patients with scalp sarcoma treated at a provincial cancer care institution.

Methods: Subjects were 95 patients referred between the years 1990-2015 with a primary diagnosis of scalp sarcoma. Chart review was performed to extract data on demographics, tumor and treatment characteristics. Kaplan-Meier (KM) statistics were used to estimate local relapse-free survival (LRFS) and overall survival (OS). Survival curves were compared using log-rank tests.

Results: Median follow-up time was 33.1 months (range 1.5 to 255.8 months). Median age at diagnosis was 77 years (range 19 to 96 years). The most common histologic subtypes were Angiosarcoma (27%), Undifferentiated Pleomorphic Sarcoma (24%), and Pleomorphic Dermal Sarcoma (21%). Excisional biopsy was performed in 61% of patients as initial surgery. Among 54 patients who underwent re-excision after initial biopsy, 16 (30%) required tissue flap and 28 (52%) skin graft. Final margin status were: 36% (n=34) positive, 28% (n=27) close <3mm, 31% (n=29) negative, and 5% (n=5) unknown.

Medeoriju survival was 54 months (range 1.5 to 256 months). Five-year KM LRFS was 56.0% (95% CI: 42.1-67.7%) and OS 48.3% (95% CI: 36.9-58.8%). Of 73 patients initially treated with curative-intent, 32 (44%) had a LR. On subset analysis, 5-year KM LRFS estimates were 36.8% (95% CI: 16.4-57.5%) with positive margins, 81.4% (95% CI: 56.7-92.8%) with close margins, and 59.4% (95% CI: 35.3-77.0%) with negative margins, log-rank p=0.008. Patients with close or positive margins who received pre- or postoperative RT (n=19) had similar LR risk compared to patients who did not receive RT (n=34) (5-year KM LRFS 41.8% vs 69.1%; log-rank p=0.145). On univariate analysis, angiosarcoma was significantly associated with higher LR risk compared to other histologies (HR 4.81, 95% CI 2.34-9.87, p<0.001). Age, re-excision surgery, and RT use were not significantly associated with LR. A trend for higher LR was observed with close/positive margin compared to negative margin but this was not statistically significant (HR 1.48, 95% CI: 0.69-3.18, p>0.05).

Conclusion: Patients with scalp sarcoma have high risks of local relapse, particularly in cases with positive margins. Adjuvant radiation was not associated with improved local control for close or positive margins. Complete surgical excision establishing negative margins remains the primary standard treatment for patients with this rare disease.
9. IDENTIFYING DNA BIOMARKERS OF BACILLUS CALMETTE-GUERIN (BCG) RESISTANCE IN NON-MUSCLE-INVASIVE BLADDER CANCER

Bacon J.V.W.*, Vandekerkhove G., Annala M., Mueller D.C., Rentsch C.A, WYATT A.W.

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Category: Translational/Clinical

Background: Bacillus Calmette-Guerin (BCG) therapy is the gold standard of treatment for non-muscle-invasive bladder cancer (NMIBC). However, clinicopathological factors predicting response to BCG remain limited in scope and utility. Despite high initial efficacy, 60% of cases experience local recurrence or progress to muscle-invasive bladder cancer (MIBC). Establishing genetic biomarkers for predicting treatment response will be vital to improving NMIBC patient outcomes.

Methods: Archived formalin-fixed, paraffin-embedded tissue sections were obtained from 12 relapsed NMIBC patients and 8 BCG responsive patients. Of the 12 relapsed patients, six had an NMIBC recurrence and six showed MIBC progression. We performed targeted DNA sequencing of 50 relevant bladder cancer genes on all samples. Relapsing patients each had samples from both pre- and post- BCG initiation, while responding patients only had pre-BCG samples available.

Results: FGFR3 and KMT2D mutations were enriched in the pre-BCG cohort relative to the post-BCG cohort (21% vs. 0% and 32% vs. 8%) while TP53 mutations were enriched post-BCG (57% vs. 75%). We identified two BCG responders with somatic hypermutation, each featuring over 30 mutations per MB. Lastly, 5/12 relapsed patients had a major somatic clonal switch over the course of BCG treatment indicative of strong selective pressure by BCG.

Conclusions: Resistance to BCG and progression of NMIBC to MIBC may be linked to loss of tumour suppressor genes and baseline clonal heterogeneity. Temporal changes at relapse or progression are suggestive of dramatic clonal shifts in response to therapy, despite uniform presence of a common ancestral clone. Further accrual and sequencing are ongoing.
10. MANAGEMENT OF GLIOBLASTOMA IN THE ELDERLY - A 10 YEAR ANALYSIS OF THE BC CANCER AGENCY POPULATION

Zeng J. (trainee – Medical student), KRAUZE A.

Category: Population Health/Health Services

**Purpose:** Glioblastomas (GBM) are the most common primary tumours of the brain and carry an extremely poor prognosis. Despite recent publications, management of the elderly remains heterogeneous. We investigate the impact of patient characteristics and treatment modalities on the outcome of elderly patients with GBM in British Columbia (BC) from 2005-2015.

**Methods:** Using the BC Cancer Agency patient registry, 822 adults diagnosed from 2005-2015, ≥ age 60 with histologically confirmed GBM ICD-O-3 codes (9440/3, 9441/3, 9442/3) were identified. Univariate, multivariate and Kaplan-Meier analyses were performed on patient characteristics and treatment modalities for overall survival (OS).

**Results:** Median OS was 6.57 months (0.03-99.93). 60% of the patients were male, mean age at diagnosis was 70 (60-90). Patients were aged 60-64 (26%), 65-69 (27%), 70-74 (20%), ≥75 (27%). 65% of the cohort was diagnosed between 2011-2015 (35%) vs. 2005-2010 (65%). 96% of patients had a diagnosis of glioblastoma with the remainder giant cell glioblastoma and gliosarcoma. MGMT promoter methylation status was available in 11% of patients. Resection status was GTR/STR (72%), biopsy (28%). 41% of patients received chemotherapy, 77% of patients received radiation therapy (RT). 20% of patients did not receive treatment beyond surgical intervention. Patient management involved concurrent chemoirradiation (CRT) (40%), RT alone (37%), chemo alone (1.5%). Younger patients aged 60-69, concurrent CRT and maximal safe resection (GTR/STR) resulted in improved OS (p<0.0001). Year of diagnosis and RT dose fractionation (60/30 (38%) vs. 40/15 (36%)) were not associated with a difference in OS.

**Conclusion:** Elderly patients with GBM treated in BC 2005-2015 achieved similar outcomes to those of existing published data. Younger age, aggressive resection and concurrent CRT were associated with improved OS. Ongoing analysis is directed at further correlation of patient and treatment factors, features of RT and chemotherapy administration, progression-free survival and patterns of failure.
11. SYSTEMIC THERAPY AFTER PROGRAMMED DEATH-1 RECEPTOR ANTIBODY (PD1 AB) FAILURE IN ADVANCED NONSMALL CELL LUNG CANCER (ANSCLC)

KSIENSKI D.1, Lesperance M.2, Croteau N.1, Fiorino L.1, Poonja Z.1, Geller G.1, Fenton D.1, Brooks E.1, Wai E.S.1, Freeman A.1

1BC Cancer-Victoria, 2University of Victoria

Category: Translational/Clinical

Background: The PD1 Ab nivolumab (N) and pembrolizumab (P) are now standard of care for a subset of patients (pts) with aNSCLC; however, only a small proportion of pts will have a prolonged response. The efficacy of systemic therapy after progression on PD1 Ab is not known.

Methods: All aNSCLC pts initiated on N or P between 11/2015 to 10/2017 at BC Cancer with subsequent progression were identified. Retrospective chart review was conducted from initial referral to death or last follow-up. Fisher’s exact test was used to compare baseline characteristics amongst pts who received systemic therapy after PD1 Ab versus no subsequent treatment. Kaplan-Meier (KM) curves of overall survival (OS) from initiation of drug post-PD1 Ab were generated. Progression free survival (PFS) from start of post-PD1 Ab therapy until last dose or death were estimated by KM method.

Results: Of 141 pts who progressed on N or P, 33 received subsequent systemic therapy. Characteristics of cohort: median age 64.0y (range 56.0-70.0), male: 42.4%, primary histology: squamous 24.2%, Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2 at start of PD1: 18.2%, liver metastases (mets) at diagnosis: 12.1%, brain mets at diagnosis: 9.1%, and EGFR mutation: 9.1%. 81.8% had progressed on N, PD1 Ab was delivered as a first or second line treatment in 78.8% of pts, and median PD1 Ab cycles delivered was 8.0 (range 6.0-11.0). Post PD1 Ab treatment: erlotinib (n=10), docetaxel (n=8), pemetrexed (n=7), platinum doublet (n=4), vinorelbine (n=2), ceritinib (n=1), and gefitinib (n=1). Pts not receiving subsequent treatment had worse ECOG PS at start of PD1 Ab (P=0.001), higher Charlson Comorbidty Index (P=0.017), and received fewer PD1 Ab cycles (P<0.001). At last follow-up, 23 (70.0%) pts had died. Median PFS and OS from initiation of post-PD1 Ab therapy was 1.7 months (95%CI, 0.9-2.8) and 6.7 months (95%CI, 3.5-12.2), respectively. 32 (97.0%) pts receiving systemic therapy progressed.

Conclusions: 23.4% of pts who progressed on PD1 Ab (mainly nivolumab) received subsequent treatment. In the study cohort, PFS was lower than expected for a second or third line treatment of aNSCLC. Further study is required to determine predictive biomarkers to systemic therapy after PD1 Ab progression.
12. THE MYXOID LIPOSARCOMA FUSION PROTEIN FUS-DDIT3 ASSOCIATES WITH CHROMATIN REGULATORS

Yu J., Colborne S., Goytain A., Morin G., Nielsen T.

TFRI Project: Genomics of forme fruste tumours: new vistas on cancer biology and management (Project leader: DAVID HUNTSMAN)

Category: Biology/Informatics

Myxoid liposarcoma is a malignant fatty tumour that often develops in the deep soft tissue. While local disease is well controlled with surgery and radiotherapy, current chemotherapy options remain ineffective against metastatic disease, and there is an urgent need to identify specific targeted therapies. Myxoid liposarcoma is driven by a balanced translocation involving FUS (12q13) and DDIT3 (16p11). Although the resulting FUS-DDIT3 oncoprotein has been proposed to form an aberrant transcriptional complex, its exact mechanism of action has remained unclear, rendering it difficult to formulate rational strategies for targeted therapy. The lack of comprehensive data on the FUS-DDIT3 interactome represents one of the major gaps in knowledge behind the oncogenic functions of FUS-DDIT3. This study utilized immunoprecipitation-mass spectrometry and tandem mass tag-labeling to identify FUS-DDIT3’s key interactors from nuclear extracts of myxoid liposarcoma cells. Members of several chromatin regulatory complexes were identified, including the NuRD, SWI/SNF, PRC1, PRC2 and MLL1 COMPASS-like complexes. Further co-immunoprecipitation experiments validated the association of FUS-DDIT3 with BRG1/SMARCA4, BAF155/SMARCC1, BAF57/SMARCE1, HDAC2, KDM1A, and MTA1. H3K27ac levels at the promoter of a gene target, PTX3, were also reduced after FUS-DDIT3 knockdown. Other sarcoma fusion oncoproteins (EWS-FLI1, SS18-SSX and PAX3-FOXO1) have recently been reported to interact with chromatin regulators and employ alterations of histone modifications or chromatin remodeling as one of their oncogenic mechanisms. FUS-DDIT3 may utilize a similar epigenetic mechanism of action, providing potential candidates for targeted therapy since epigenetic aberrations are potentially reversible by emerging epigenetic drugs.
13. DETECTION OF CIRCULATING TUMOR DNA IN DE NOVO METASTATIC PROSTATE CANCER

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Category: Translational/Clinical

Background: De novo metastatic disease accounts for 5-10% of prostate cancer diagnoses, but nearly 50% of disease-related deaths. Patients may benefit from treatments other than androgen deprivation therapy (ADT), including targeted or combination therapies. There is potential for tumor molecular biomarkers to aid in guiding patient clinical management, however patients with de novo metastatic disease seldom undergo prostatectomy and thus tumor tissue is often only available from their diagnostic biopsy. We aimed to determine the utility of plasma circulating tumor DNA (ctDNA), a promising biomarker source in the castration-resistant setting, in metastatic castration-sensitive prostate cancer (mCSPC).

Methods: Whole blood samples were collected at time of diagnosis from 53 de novo mCSPC patients. Targeted DNA sequencing was successfully performed across 73 prostate cancer relevant genes for 52/53 ctDNA samples, and 48/53 had matched tumor tissue available.

Results: Blood was collected from 35/53 patients prior to ADT initiation, while 18/53 had received 1-49 days of ADT. ctDNA levels were significantly impacted by castration therapy, with detectable ctDNA in 26/35 ADT-naive patients compared to 10/17 who had received ≥1 day of ADT (mean ctDNA fraction 23.3% vs 6.7%, p=0.024, ranksum test). All eight patients with visceral metastases (lung/liver) had detectable ctDNA, regardless of prior ADT exposure. We found no relationship between ctDNA and PSA, Gleason score, or age at diagnosis. Our analysis reveals an aggressive genomic landscape surprisingly similar to metastatic castration-resistant prostate cancer, though lacking in AR alterations (in accordance with castration-sensitive disease). Somatic alterations were highly concordant between matched plasma and tissue samples.

Conclusions: The majority of de novo mCSPC patients have detectable plasma ctDNA at diagnosis. ctDNA is increased in treatment-naïve patients and those with visceral metastases. Concordance between diagnostic tissue and plasma is high; tissue-based and ctDNA analyses are complementary and should both be utilized in assessing the somatic landscape of de novo mCSPC.
CIRCULATING TUMOR DNA PROFILING REVEALS A DEFICIENCY OF BIOMARKERS PREDICTIVE OF DOCETAXEL RESPONSE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Background: Docetaxel chemotherapy is a standard of care for men with metastatic castration-resistant prostate cancer (mCRPC). However, therapeutic benefit is eclipsed by the inevitability of resistance—45% of patients do not respond, and all will eventually relapse. There are currently no established markers to predict whether patients will respond to docetaxel. Herein lies an urgent clinical need for biomarkers predictive of docetaxel response, thereby allowing patients earlier access to potentially effective therapies while avoiding the unnecessary toxicity of taxane treatment.

Methods: Our objective was to identify molecular biomarkers in plasma cell-free DNA (cfDNA) that are associated with docetaxel therapy response. We enrolled a prospective cohort of 58 mCRPC patients who had progressed on androgen receptor (AR) targeted agents but had not received prior taxane therapy. A blood sample for cfDNA analysis was collected before initiation of docetaxel, and targeted sequencing of 73 prostate cancer-relevant genes was performed on both leukocyte (germline) and plasma cfDNA. Patient records were reviewed for baseline clinical characteristics, PSA response (≥50% decline from baseline), and time to PSA progression (TTPP) (PCWG3 criteria) on docetaxel. Clinical outcomes were correlated with circulating tumour DNA (ctDNA) fraction and the genomic status of key prostate cancer genes.

Results: We identified frequent disruption to TP53 (20/58, 35%), PTEN (14/58, 24%), and RB1 (11/58, 19%), as well as recurrent AR copy number amplification (24/58, 41%). The majority of the cohort had >2% ctDNA in their plasma sample (39/58, 67%). Of the 52 patients for which clinical outcomes were assessed, the median TTPP was 3.93 months, and 38.4% (20/52) experienced a PSA response. No significant relationships with either PSA response or TTPP were identified among genomic factors previously implicated in response to AR-targeted drugs. Many of the same genomic variables, however, display a clear association with patient overall survival, consistent with previous reports of their prognostic utility in mCRPC.

Conclusions: These findings point to lack of relationship between common prostate cancer molecular subtypes and taxane therapy response in mCRPC. However, this analysis does not address the role of regulatory or epigenetic mechanisms, nor rarer somatic alterations not covered by our gene panel. Nevertheless, since genomic factors such as TP53 mutations and AR amplifications are linked to lack of mCRPC response to abiraterone and enzalutamide, our study suggests that patients that are unlikely to respond to AR-targeted therapy may instead benefit from docetaxel.
Fluorescent in situ hybridization (FISH) is a high-volume test in the clinical Cancer Genetics and Genomics laboratory and is the preferred technique to identify gene amplification, deletion, and structural rearrangement events in cancer specimens. FISH provides information essential for diagnostic, prognostic and therapeutics; however, it is beset by its low throughput workflow due to its heavy reliance on manual recording and calculating individual fluorescence signals.

Our project explores the implementation of an automated FISH workflow at CGL. The goals of this project are to increase the efficiency of the FISH assay, digitize the FISH probe database, and improve record-keeping for quality control. Our automated FISH counter aims to replace the current workflow with an all-in-one Microsoft Excel solution and an integrated ergonomic one-handed keyboard. The Excel component consists of a worksheet template page and a digital database including all the information on typical signal patterns and cut-offs for actively used FISH probes at CGL. The new workflow allows the technologist to select a probe then automatically populates the probe information and formats itself into a printable form. Additionally, this new worksheet template will automatically alert the technologist when the probe counts are outside the laboratory’s established quality metrics. This automated FISH counter will seek to improve record-keeping for quality control assessments by tracking the hybridization quality history of each test.

The automated workflow uses the advantages of digital systems to increase the efficiency of the FISH assay. After more the 1800 lines of code, it is expected to enter clinical use and will continue to gain feedback from the end users. We hope this project will reveal the streamlining potential of digitized workflows in the clinical molecular pathology laboratory.
16. **CRL2\(^{\text{VHL}}\) COMPLEX DISRUPTIONS ARE ASSOCIATED WITH PATIENT PROGNOSIS IN LIVER CANCER**

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* Presenting author is a graduate student.

**Category: Translational/Clinical**

**Background:** Loss-of-function mutations in \(\text{VHL}\) (a component of the CRL2\(^{\text{VHL}}\) complex \([\text{ELO(B/C)/CUL2/VHL}]\)) is a common event in several cancers. It constitutively activates \(\text{HIF-1}\alpha\), triggering abnormal hypoxic responses. In hepatocellular carcinoma (HCC), \(\text{VHL}\) remains unaltered, while aberrant expression of \(\text{ELOC}\) is found in over 30% of cases. However, the causes and consequences of this deregulation remain poorly understood. Therefore, this study aims to explore the mechanisms of \(\text{ELOC}\) upregulation in HCC.

**Methods:** We analyzed 364 non-malignant/tumour liver samples obtained from TCGA. Small RNA-seq data were used to identify aberrantly expressed annotated and unannotated miRNAs in \(\text{ELOC}\)-dysregulated HCC cases unexplained by CNA or promoter hypomethylation. Finally, gene-target prediction and pathway enrichment analyses were used to confirm the relevance of the unannotated miRNAs.

**Results:** \(\text{ELOC}\) showed the highest frequency of CNA (11.4%) and increased expression levels when compared against normal samples (FC=1.7; \(p=2.0\times10^{-21}\)). Additionally, \(\text{ELOC}\) promoter hypomethylation was observed in 41% of HCC tumours (\(\Delta\beta=-0.12; p=2.0\times10^{-20}\)). A negative correlation (\(r=-0.39; p=3.0\times10^{-17}\)) was observed between \(\text{ELOC}\) expression and the methylation levels, yet 4% of the \(\text{ELOC}\)-overexpressing tumours did not show neither CNA nor hypomethylation. Further, 11 unannotated and 18 annotated miRNAs were significantly downregulated in tumours, illustrating potential epigenetic drivers of \(\text{ELOC}\) overexpression. Finally, survival analyses revealed that overexpression and hypomethylation of \(\text{ELOC}\) were indicative of lower overall survival in HCC (\(p=0.043, p=0.013\)).

**Conclusions:** Our results suggest that although a high proportion of \(\text{ELOC}\) disruption can be explained by CNA and promoter hypomethylation, a subset may be driven by the aberrant expression of both known and novel miRNA transcripts. As the CRL2\(^{\text{VHL}}\) complex is critical to protein turnover and tumourigenesis, elucidating the mechanisms of complex deregulation will uncover novel therapeutic targets in the treatment of HCC.
LIVER CANCER IS ASSOCIATED WITH THE REACTIVATION OF NOVEL ONCOFETAL TRANSCRIPTS


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* Presenting author is a graduate student.

Background: The reactivation of developmental signaling pathways in adult cells, as a result of mutations and epigenetic alterations, has been shown as a common feature of tumorigenesis. Genes involved in these reactivated signaling pathways may be defined as oncofetal genes. Considering that small non-coding RNAs (sncRNAs, e.g. miRNA, snoRNA, piRNA, snRNA) are key regulators of gene expression and have shown promise as fluid-based biomarkers, this study aims to identify oncofetal sncRNAs important for liver tumor biology, including the discovery of previously-unannotated miRNAs.

Methods: We analyzed small RNA-sequence data from 47 paired non-malignant/tumour liver samples processed by The Cancer Genome Atlas (TCGA), as well as 10 fetal liver samples from our internal cohort. Briefly, samples were processed by the platform miRMaster, quantifying known sncRNA species and predicting novel miRNA candidates using the mirDeep2 algorithm, a well-established novel miRNA discovery algorithm. SncRNA species that had no significant alterations in expression between fetal and tumour samples, but displayed differential expression between fetal/non-malignant and tumour/non-malignant tissues were classified as oncofetal. The biological relevance of the oncofetal sncRNAs were investigated by gene-target prediction and pathway enrichment analyses.

Results: We discovered the expression of 198 novel miRNA candidates in fetal, tumour and non-malignant liver tissues, representing a 9.3% increase to the total pool of miRNAs expressed in liver. Additionally, a total of 45 known sncRNA species and 3 novel miRNAs displayed the oncofetal expression pattern. Target prediction analysis showed that the novel miRNA candidates are involved with cell cycle, transcriptional regulation and ERK signaling.

Conclusion: We have not only expanded the liver small-RNA transcriptome, but also revealed the expression of oncofetal sncRNAs relevant to liver tumourigenesis. Therefore, our results may aid to the development of more accurate fluid-based biomarkers for the early-detection of liver cancer.
SURFACE MOULD BRACHYTHERAPY FOR SKIN CANCERS: THE BC CANCER EXPERIENCE

Casey S. (Radiation Oncology fellow), Awotwi-Pratt J., and BAHL G.

Category: Translational/Clinical

Purpose: To examine and report on the use of surface mould brachytherapy at our institution for the treatment of skin tumors.

Methods: This was a retrospective review for all patients with skin tumors treated using surface mould brachytherapy, from Jan. 1, 2010 – Dec. 31 2017, in British Columbia. We identified 65 lesions (59 patients) that were treated with Ir-192 HDR surface mould brachytherapy. Median age at diagnosis was 83 (range = 45 – 97). The majority were basal cell carcinomas (54%, n=35) and 31% (n=20) were squamous cell carcinomas. The most common site was the forehead or temple (30%, n=19), 23% on the nose, 22% were on the scalp, 17% on the cheek or lip, and 6 lesions were miscellaneously located. The most commonly used RT dose was 40Gy/10; all patients had individualized CT-based planning.

Results: The 2 year overall survival (OS) was 77.6% and 2 year progression free survival (PFS) was 71.5%. Most deaths were due to unrelated causes. Response was assessed in clinic around 2 – 4 months after treatment. Our complete response (CR) rate was 96.8%, and partial response was seen in 2 patients; 2 patients could not be assessed for response. There were no stable or progressive lesions. We report a 2 year Local Control (LC) rate of 84.9%, with recurrence at the treated site in 5 patients. The procedure was well tolerated and there was no Grade 3 – 5 toxicity acutely or long-term. There was only 1 case of Grade 2 radionecrosis (CTCAE v. 4.03). The median depth of 100% isodose line was 0.5 cm, and the median surface dose = 126.5%. The median V90 = 92.3% and median V95 = 84.7%.

Conclusion: Surface Mould Brachytherapy for skin tumors is a safe and effective modality, with excellent response rates. It is well-tolerated and a non-invasive option that can also be used as a palliative tool for elderly patients with comorbidities.

Conflicts of interest: Dr. Bahl participated on Advisory Board Meetings for Sanofi and Bayer – otherwise, there are no disclosures.
19. EFFICACY OF PALLIATIVE RADIATION THERAPY (RT) FOR DIFFUSE LARGE B-CELL LYMPHOMA: A POPULATION-BASED RETROSPECTIVE REVIEW

Wong J. (Resident), Pickles T., Connors J., Aquino-Parsons C., Sehn L., Freeman C., DeVries K., LO A.

Category: Translational/Clinical

Background: Previous studies suggest that refractory/relapsed diffuse large B-cell lymphoma (DLBCL) may require higher doses of radiation, and the optimal palliative radiotherapy (RT) dose is unclear. The aim of this study was to investigate the effectiveness of palliative RT for refractory/relapsed DLBCL patients and to identify factors that may influence RT response rates and/or time to local progression.

Methods: All patients with DLBCL who received palliative RT from 2001-2015 in British Columbia were reviewed for patient characteristics, treatment details, and outcomes. Univariable and multivariable analyses of factors associated with clinical and/or radiological response were performed using logistic Generalized Estimating Equation (GEE) method. Univariable and multivariable analyses of factors associated with local control were performed using Kaplan Meier survival curves and Cox regression hazard models. Only the first radiation course was included per patient for local control analyses.

Results: Two hundred and seventeen patients who received 370 courses of palliative RT were identified. Median age at RT was 76 years (range 25-103 years), and 57% of courses were in male patients. Median equivalent dose in 2 Gray fractions was 19 Gy (2-42 Gy); dose fractionation ranged from 2 Gy in 1 fraction to 40 Gy in 15 fractions. Size of treated lesion was documented in 240 courses, of which median largest dimension was 5.8 cm (range 0.5-30 cm). Most commonly treated site was skin (22%) and the most common indication for RT was pain (42%). Clinical response assessment was available for 274 courses (74%), of which 42 courses had radiologic follow up; 2 courses had only radiologic response assessments. Symptom resolution was achieved in 42% of courses (114/274), symptom improvement in 40% (110/274), and stability in 13% (36/274); there was symptom progression in 5% (14/274). Factors observed to be associated with higher likelihood of clinical and/or radiological response to palliative RT on multivariable analysis included response to first line chemotherapy (OR 2.6, \(P=0.03\)), not requiring concurrent steroids during palliative RT (OR 5.3, \(P=0.001\)), and lesion size <5.8 cm (OR 3.4, \(P=0.03\)). Local control following palliative RT at 6 months was 63.0% (SE 5.1%) when only the first course of palliative RT for each patient was considered and was 67.2% (SE 3.8%) when all 370 courses were considered. On the multivariable analysis for local control, the only factor remaining in the final model was response to first line chemotherapy; hazard ratio was 4.3 (95% CI 2.1-8.5) for those who did not respond vs did respond to first line chemotherapy (\(P=0.0005\)). Initial stage I/II vs III/IV was also significantly associated on univariable analysis for both clinical and/or radiological response (OR 5.1, \(P=0.0005\)) and for local control (76% vs 55%, \(P=0.02\)).

Conclusions: Palliative RT for DLBCL is effective for symptom improvement and local disease control. Factors that predicted for poorer response rates and local control included, stage III/IV disease on presentation, no response to first line chemotherapy, and target lesion size >5.8cm at the time of RT. There was no association between dose fractionation and response rates or local control to suggest that higher palliative RT doses are warranted in DLBCL.
VALIDATION OF DEEP LEARNING BASED AUTO-SEGMENTATION METHODS FOR ORGANS AT RISK AND CLINICAL TARGET VOLUMES IN RADIOTHERAPY PLANNING

Wong J. (Resident), Smith S., McVicar N., Wells D., Giambattista J., Fong A., ALEXANDER A.

Category: Translational/Clinical

Background: The goal of radiotherapy (RT) involves maximal irradiation of specific target structures defined by clinical target volumes (CTV), while minimizing dose to organs at risk (OAR). Manual contouring of target structures on computed tomography (CT) images is a labour intensive and time consuming process necessary for RT planning. Deep learning (DL) based auto-segmentation models can improve RT planning, but validation in clinical settings is limited. The aim of this study was to compare the performance of a DL based auto-segmentation software against expert manual contours for common OARs and CTVs used in RT planning.

Methods: Three experienced Radiation Oncologists (RO) contoured the OARs and CTV for 43 patients who received RT for a central nervous system (CNS), head and neck (H&N), or prostate malignancy. Automated deep-learning based contours were generated using the DL software Limbus Contour on a consumer grade CPU. Dice similarity coefficient (DSC) and 2mm Hausdorff distances (HU) were used to compare contours. Automated and manual contouring times were recorded and statistical analysis was performed using Wilcoxon Signed Ranks test.

Results: The mean DSC from comparing RO to RO contours and Limbus to RO contours were 0.82 (standard deviation [SD] 0.06) and 0.84 (SD 0.04) for brainstem, 0.39 (SD 0.12) and 0.43 (SD 0.06) for optic chiasm, 0.51 (SD 0.07) and 0.54 (SD 0.10) for optic nerve, 0.82 (SD 0.04) and 0.81 (SD 0.06) for parotid gland, 0.84 (SD 0.04) and 0.83 (SD 0.04) for submandibular gland, 0.79 (SD 0.02) and 0.71 (SD 0.02) for neck lymph node CTV, 0.85 (SD 0.05) and 0.81 (SD 0.04) for prostate CTV, 0.68 (SD 0.09) and 0.72 (SD 0.07) for seminal vesicle CTV, 0.81 (SD 0.08) and 0.84 (SD 0.06) for rectum, and 0.97 (SD 0.01) and 0.97 (SD 0.01) for bladder. The mean 2mm HU from comparing RO to RO contours and Limbus to RO contours were 32.7 (SD 8.2) and 31.5mm (SD 7.0) for brainstem, 55.4 (SD 10.9) and 56.3mm (SD 6.8) for optic chiasm, 36.7 (SD 7.1) and 35.4mm (SD 11.3) for optic nerve, 33.3 (SD 6.6) and 37.1mm (SD 6.5) for parotid gland, 22.4 (SD 9.5) and 25.7mm (SD 8.8) for submandibular gland, 37.2 (SD 7.4) and 54.4mm (SD 5.8) for neck lymph node CTV, 41.1 (SD 9.5) and 53.6mm (SD 10.9) for prostate CTV, 41.9 (SD 8.8) and 39.8mm (SD 6.6) for seminal vesicle CTV, 28.3 (SD 7.7) and 28.3mm (SD 8.5) for rectum, and 18.3 (SD 4.1) and 18.1mm (SD 8.8) for bladder. Average time for ROs to contour compared to Limbus was 8.0 vs 1.1 minutes (Z = -3.9, p < 0.001) for CNS radiotherapy plans, 27.8 vs 2.7 minutes (Z = -3.2, p = 0.001) for H&N plans, and 21.8 vs 1.4 minutes (Z = -2.8, p = 0.005) for prostate plans.

Conclusions: DL based OAR contours are within RO inter-observer variability and require significantly less time to produce. DL based CTV contours also performs close to RO inter-observer variability, but may require subsequent manual edits. Implementation of DL based auto-segmentation software into clinical workflow can improve RT contouring time and reduce RT planning bottlenecks. Further evaluation of DL in this setting is necessary to determine prospective workflow benefits and the impact on dosimetric consistency.
21. INVESTIGATING THE ROLE OF ATG4B IN TREATMENT RESPONSE OF HER2+ BREAST CANCERS

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Category: Translational/Clinical

Breast cancer is a leading cause of cancer-related deaths among Canadian women. Approximately 20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2), a protein that initiates signaling events supporting cell growth and survival. Although anti-HER2 therapies, like trastuzumab (Tz), have significantly improved patient survival, treatment resistance in advanced cases of HER2+ cancers has not yet been effectively addressed. Recent studies have uncovered a novel positive association between HER2 and autophagy-related 4B (ATG4B), a cysteine protease that functions in the cell survival process of autophagy. HER2 overexpression increases ATG4B levels, and ATG4B inhibition increases the sensitivity of HER2+ breast cancer cell lines to Tz. Understanding the mechanisms behind how HER2 regulates ATG4B and how ATG4B inhibition promotes chemosensitivity is necessary for developing rational strategies to combat treatment resistance in HER2+ cancers. The overall objectives of my project are to understand the functional relationship between ATG4B and HER2, and to evaluate the potential of increasing the sensitivity of resistant HER2+ breast cancers to anti-HER2 agents by inhibiting ATG4B. To do so, I will investigate the mechanistic link between HER2 and ATG4B using targeted proteomic analyses (affinity-purification mass spectrometry). I will also evaluate the potential of ATG4B inhibition in sensitizing HER2+ breast cancers to Trastuzumab using CRISPR/Cas9 gene editing and cell line-derived xenograft (CDX) models. Together, these studies have the potential to develop new therapeutic targets/combination strategies for HER2+ breast cancers, and validate in vivo ATG4B inhibition as a therapeutic approach for treatment-resistant HER2+ cancers.
PROTEIN TYROSINE PHOSPHATASE ALPHA (PTPα) IS CRITICAL FOR LOCAL CANCER CELL INVASION

Decotret L.1,2,4,* Li L.2,4, Lim C.J.2,3, Bennewith K.1,4, and Pallen C.J.2,3,4

1BC Cancer Research Centre; 2BC Children’s Hospital Research Institute; 3Department of Pediatrics; 4Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver BC, Canada. *Graduate student

Category: Translational/Clinical

Metastasis has been estimated to account for over 90% of cancer-related deaths. Despite great efforts, there has been limited improvements made over the past few decades outlining a critical need for early detection and intervention. Some cancer cells have acquired the ability to move throughout the body through the formation of specialized structures called invadopodia ("invasive feet"). Invadopodia are classified as dynamic Src-regulated, actin-based protrusions of the plasma membrane that secrete matrix metalloproteases (MMPs) to degrade the surrounding extracellular matrix (ECM). Protein tyrosine phosphatase alpha (PTP), a widely expressed transmembrane protein, acts in normal cells to promote cell migration via the formation of similar structures called focal adhesions. However, little is known about the role of PTP in cancer cell motility.

We propose a new role for PTPα in regulating invadopodia function to promote the invasive motility of malignant cells.

PTP knockdown MDA-MB-231 cells showed reduced migration and invasion compared to the control, which was rescued upon reintroduction of PTP suggesting PTP promotes tumour cell migration and invasion. Matrix degradation assays revealed that PTPα-depleted cells are impaired in their ability to degrade ECM compared to the control. Interestingly, control and PTPα-depleted cells formed equivalent numbers of invadopodia, and PTPα co-localized with cortactin, actin, and MT1-MMP to invadopodia-like structures. Together, these findings indicate that PTPα present within invadopodial structures, positively regulates invadopodia-mediated ECM degradation while not altering the signaling pathways involved in invadopodia formation. Furthermore, PTP depletion decreased MMP9 expression and activity as well as cell surface expression of MT1-MMP (MMP14) outlining a possible reason for the dysfunctional invadopodia.

In summary, these results have shown that PTP is present within invadopodial structures and positively regulates invadopodia-mediated tumour cell motility. Thus, outlining a potential role for PTP in invadopodia-mediated local invasion of triple negative breast cancer cells. Future research may reveal new mechanistic targets for therapeutic intervention to prevent cancer metastasis and improve patient outcome.
23. EFFECT OF SMOKING HISTORY ON THE PERCEIVED HARM OF ELECTRONIC CIGARETTES VERSUS CONVENTIONAL CIGARETTES

Chen L.*, Wang A., CHEUNG W. (*MSc Candidate at UBC)

Category: Population Health/Health Services

Background: Electronic cigarettes (e-cigs) are rapidly gaining popularity as health policy experts advocate its role for harm-reduction among smokers and caution its potential as a gateway tobacco product. The way e-cigs are used may be associated with its perception by the public. As of 2018, understanding of the public’s opinion regarding e-cigs’ harm in various demographic groups, including smokers and non-smokers, remains poorly understood.

Method: This study combines data from six cycles of the Health Information National Trends Survey (HINTS), a nationally representative survey collected by the National Cancer Institute. Survey-weighted logistic regression models were used to evaluate the effect of smoker status on perceived harm of e-cigs compared to conventional cigarettes.

Results: Surveys included 19,251 respondents over six cycles of HINTS. Respondents tended to be 50 or older (65.5%), female (58.9%), college educated (43.2%), and employed, a homemaker, or a student (59.0%). Most respondents were non-Hispanic White (65.9%), 12.8% were African American, and 13.8% were Hispanic. Household income per year were disparate, with the largest subgroups being either those who earned $75,000 or more (32.3%) or those who earned less than $20,000 (21.5%). At 59.2%, most respondents were never smokers (NS), while 27.6% were former smokers (FS) and 14.2% were current smokers (CS).

Survey weighted tables found 57.6% of the general population believed e-cigs were as harmful or more harmful than conventional cigarettes. Among CS, FS, and NS, the proportion of respondents who believed e-cigs were at least as harmful were 44.3%, 56.7%, and 61.9% respectively. In univariate analysis, this perception was higher among FS (OR 1.644, 95%CI: 1.405-1.924) and NS (OR 2.044, 95%CI: 1.761-2.372) compared to CS. Wald-test analysis found ethnicity was the most significant modifier of this perception (p<0.001). The results of survey-weighted logistic regression with interaction terms are presented in Table 1.

Conclusion: In our analyses of a nationally representative survey, a reduced history of smoking was significantly associated with an increased perception that e-cigs are as harmful as conventional cigarettes. This suggests that public health education campaigns have been effective in promoting e-cigs among smokers while cautioning against their use in non-smokers. In stratified analysis, this trend was persistent among non-Hispanic White and Hispanic populations, but not among Non-Hispanic Black and other ethnic groups. Ethnic differences in the perception of the harm of e-cigs may have health policy implications.

Table 1. Odds of Perceiving e-Cigs are As or More Harmful than Conventional Cigarettes

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Current Smoker</th>
<th></th>
<th>Former Smoker</th>
<th></th>
<th>Never Smoker</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds</td>
<td>95% CI</td>
<td>Odds</td>
<td>95% CI</td>
<td>Odds</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td></td>
<td>Lower</td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper</td>
<td></td>
<td>Upper</td>
<td></td>
<td>Upper</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>0.665</td>
<td>0.564</td>
<td>0.784</td>
<td>1.123</td>
<td>1.011</td>
<td>1.248</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.379</td>
<td>1.271</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1.489</td>
<td>0.891</td>
<td>2.489</td>
<td>2.658</td>
<td>1.817</td>
<td>3.887</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.728</td>
<td>2.049</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.766</td>
<td>0.494</td>
<td>1.189</td>
<td>1.943</td>
<td>1.338</td>
<td>2.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.042</td>
<td>1.611</td>
</tr>
<tr>
<td>Other</td>
<td>1.482</td>
<td>0.898</td>
<td>2.447</td>
<td>1.491</td>
<td>0.873</td>
<td>2.545</td>
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<td></td>
<td></td>
<td></td>
<td>1.724</td>
<td>1.350</td>
</tr>
</tbody>
</table>
Objective: The GICOU was launched in 2004 to facilitate the use of BC Cancer data to (1) inform BC Cancer policy development through evidence-based research, (2) monitor the outcome data collection process and enhance compliance and accuracy of outcomes reporting, (3) facilitate the investigation of clinical questions using local data to inform best practices and for quality assurance, (4) facilitate the academic development of BC Cancer clinicians, scientists, residents, fellows, and students, and (5) liaise with Data Quality & Registry to ensure that data collected is relevant and accurate.

Design: The GICOU falls under the auspices of the Gastrointestinal Tumour Group (GITG). A Methods and Priorities group approves and monitors study progress.

Materials and Methods: The GICOU database consists of audited demographic, staging, pathology, treatment, and outcome data for over 26,000 colorectal cancer patients and referred to BC Cancer. Also included are over 2,000 referred patients diagnosed with neuroendocrine tumours (NETs) and over 1,400 referred patients diagnosed with pancreatic carcinoma. The data is population-based and is prospectively collected. Investigators pose clinical questions in the form of project proposals, which are evaluated by the Methods and Priorities group in terms of scientific merit and methodology. Once GICOU and REB approval have been obtained, the cohort is assembled, data audited for quality, and analyses performed. Results are written and submitted for publication and/or conference presentation.

Results: Over 65 published abstracts and 57 peer-reviewed manuscripts have been published/submitted to date. Study results have helped to guide local treatment policy by identifying staging and prognostic factors useful in steering locoregional management as well as through the evaluation of the benefit of various chemotherapy regimens in the treatment of colorectal cancer, pancreatic cancer, and NETs. Collaborations include the Centre for Translational and Applied Genomics (CTAG), BC Cancer Research Centre, University of Manitoba, Canadian Centre for Applied Research in Cancer Control and the Mayo Clinic. Two tissue microarrays (TMAs) have been developed for biomarker studies.

Conclusions: Study results have directly influenced BC Cancer treatment policy and supported therapeutic program changes at BC Cancer. The GICOU is providing an essential clinical component to translational and molecular marker research at BC Cancer. The Unit also provides information, upon request, that informs decisions on the need for, and utilization of, various interventions for colorectal, NET, and pancreatic cancer patients.
Objectives: With rising cost of healthcare, clinicians are constantly challenged with balancing the best medical and safety decisions while maintaining fiscal responsibility. Difficult choices may have to be made to implement improvement initiatives lower on the hierarchy of effectiveness due to cost reasons. BC Cancer Pharmacy was asked to develop a process to find the balance between safety and cost savings when determining parenteral medication inventory line items stocked at BC Cancer and to identify other mechanisms to prevent vial strength selection errors.

Design: The Pharmacy team examined the drug inventory addition process from multiple lenses—clinical, operations, cost, drug characteristic, drug dosage form design and human factors. The review helped identify upstream and downstream processes that required further review.

Results: “Decision tree for adding parenteral medication line item to BC Cancer inventory” was developed, piloted and incorporated into standard work. Recommendations on future quality improvement work were developed.

Conclusion: The tool developed in this project is the first step in navigating the complex drug inventory management process. More research is required to develop a safety vs cost calculator to help guide future decisions.
26. TARGETING STRESS GRANULES BLOCKS SARCOMA METASTASIS

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Department of Molecular Oncology, British Columbia Cancer Research Centre, Vancouver, BC, Canada

Category: Biology/Informatics

The single-most powerful predictor of poor outcome in sarcoma patients’ is the presence of metastatic disease. This highlights the critical need to identify new factors that drive sarcoma metastasis. Sarcoma cells are continually exposed to acute stress within the tumor microenvironment, including oxidative and genotoxic stress, hypoxia, nutrient deprivation, or stress due to toxic therapy, each of which is potentially lethal unless tumor cells can acutely adapt to them. Successful adaptation can then lead to emergence of clones with aggressive capacity, including metastatic capacity. We and others believe that a major component of stress-induced cell plasticity is mediated through acute changes in mRNA translation. Under microenvironmental stress, cells block global mRNA translation to preserve energy, while maintaining selective translation of mRNAs that support survival under stress. One highly conserved mechanism for the former is to sequester the majority of mRNAs into cytosolic aggregates called stress granules (SGs). We recently found that the YB-1 RNA binding protein translationally activates \textit{HIF1A} mRNAs, increasing HIF1a synthesis and driving childhood sarcoma metastasis (El-Naggar et al, \textit{Cancer Cell}, 2015). Previous studies had shown that YB-1 also translationally induces Snail and Twist expression to drive a breast cancer EMT, but that YB-1 represses translation of other growth-related messages. To look for a common underlying mechanism, we analyzed mass spectrometry data from Ewing sarcoma cells +/− genetic knockdown of YB-1. This identified GTPase Activating Protein (SH3 Domain) Binding Protein 1 (G3BP1) as being upregulated by YB-1 in sarcoma cells under oxidative stress (Somasekharan et al, \textit{J Cell Biol}, 2015). G3BP1 is a stress granule (SG) nucleating protein critical for SG assembly under diverse stresses. SGs are cytosolic structures containing stalled translation initiation complexes, RNA binding proteins including G3BP1 and YB-1, the 40S ribosome, and silenced mRNAs. YB-1 directly binds to the 5’-UTR of \textit{G3BP1} mRNAs to induce its acute translation and acute G3BP1 synthesis in sarcoma cells, leading to stress-mediated SG formation. Genetically blocking either YB-1 or G3BP1 in sarcoma cells dramatically inhibits SG formation in vitro in response to oxidative stress, and dramatically inhibits metastasis of sarcoma and other tumor cells in vivo, indicating that SG formation is critical for in vivo tumor invasion and metastasis. This led us to assess whether targeting SGs might be a rational treatment strategy for human sarcomas, particularly in combination with SG inducers. We therefore performed small molecule screens for SG inhibitors, revealing several unexpected categories of SG inhibitors. We find that SG formation can be virtually eliminated in sarcoma cells using several agents currently in clinical trials for different tumor types. In mice bearing Ewing sarcoma or osteosarcoma xenografts, these agents blocked local invasion of sarcoma cells, and dramatically inhibited metastasis of sarcoma cells to lungs in these mice. These data suggest an exciting new strategy to target human sarcoma invasion and metastasis though inhibition of SGs.
27. IDENTIFYING THE LETHAL ANCESTRAL CLONES OF METASTATIC DISEASE IN PRIMARY PROSTATE CANCER

Warner E.1*, Nurminen A.2, Herberts C.1, Struss W.1, Fazli L.1, Annala M.2, Chi K.1,3, WYATT A.1

1Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada; 2Institute of Biosciences and Medical Technology, Tampere, Finland; 3Department of Medical Oncology, British Columbia Cancer Agency, British Columbia, Canada. *Graduate student

Category: Translational/Clinical

Background: Localized prostate cancer (PCa) is managed with surgery or other local interventions, but ~10% of men relapse and develop metastatic PCa (mPCa). Although primary prostate cancer is often multifocal with multiple genetically distinct clones, it is unclear how disease progresses from this stage to mPCa which is typically more homogeneous with a major dominant tumor clone.

Experimental Design: We obtained metastatic ctDNA and matched DNA from archival prostate tumor tissue collected at time of radical prostatectomy from 13 patients who developed lethal mPCa after initial localized diagnoses. All distinct tumor foci within each patient’s primary tumor were identified pathologically, and a combination of deep-targeted and whole exome sequencing was used to profile all DNA specimens.

Results: Across the 13 patients the average PSA at diagnosis was 10.23, and time between diagnosis and initiation of androgen-deprivation therapy (ADT) for metastatic disease was 3.8 years (95% confidence interval [CI] 2.06-5.60). Time from ADT initiation to development of castration-resistance was 3.58 years (95% CI 1.70-5.46). 88% of patients (with sufficient levels of ctDNA for analysis) had a clear clonal relationship between subsequent metastatic disease and at least one tumor foci within the archival primary tissue. In all instances where a TP53 mutation was detected in the mPCa setting via ctDNA, the identical TP53 mutation was present in the radical prostatectomy specimen. Of note, we observed one example of a BRCA2 truncation mutation confined to a single primary tumor foci that was completely absent from ctDNA collected at mPCa progression.

Conclusions: The ancestral somatic clones of metastatic disease were detected in the primary tumors of patients with initial localized diagnoses. Primary prostate cancer is highly heterogeneous, and multi-region sampling was necessary to identify ancestral clones as they were often confined to a lone tumor foci. Our data suggests that the driver mutations of mPCA can arise early in disease progression and could be used to identify primary tumors with high metastatic potential.
Immunotherapy agents have been shown to induce durable responses in some cancer types. High tumour mutation burden is thought to be a good predictor for response to these agents, but many patients still do not respond. Because acute myeloid leukemia (AML) and other myeloid malignancies are typified by relatively few somatic mutations, tumour mutation burden approaches are not appropriate for identifying AML patients who may benefit from immunotherapeutic approaches. Therefore, identifying novel genomic biomarkers to identify patients who will respond to immunotherapy agents could improve outcomes for AML patients.

Most next-generation sequencing approaches for identifying potential tumour neoantigens have focused on somatic mutation burden, rather than splicing variation. Recent work has shown that splicing mutations are common in patients with myeloid malignancies compared to other cancers. We hypothesized that the splicing diversity in AML presents a novel avenue for identifying patients who may respond to immunotherapy agents.

We developed an informatics pipeline for scaling inference of alternative splicing events to hundreds of RNA-Seq libraries, and applied this pipeline to hundreds of samples from multiple AML cohorts. Previously described alternative splicing events in AML such as apoptosis-inducing isoforms of \( BCL2L1 \) were confirmed in larger cohorts.

To identify potential neoantigen sequences, we will identify splice variants (such as retained introns, or alternate splice-site usage) which are recurrent within the patient cohorts, and predicted to generate neoepitope sequences. To validate that these potential neoepitopes result in novel peptide sequences, we will perform \textit{in silico} trypsin digestions to predict peptide sequences which can be detected using mass spectrometry. The validated events can then be used to identify patients who may benefit from targeted or patient-specific immunotherapeutic approaches.
Next generation sequencing has broadened our understanding of variants and genes associated with various Mendelian inherited disorders. However, not much is known about variants or genes involved in complex rare inherited diseases like lymphoid cancer. In lymphoid cancer families, different members often develop different lymphoid cancers, such as non-Hodgkin lymphoma, Hodgkin lymphoma, chronic lymphocytic leukemia and multiple myeloma, rather than always developing the same disease; implying presence of shared genetic susceptibility factors. We have 200 lymphoid cancer families with 282 affected individuals of which exome and UTR sequence from 40 lymphoid cancer families with 89 affected individuals will be used to identify these factors using our computational process. In this process, we first identify variants shared among the affected individuals of each family. These shared variants are then annotated and scored. Scoring is based on the number of affected individuals in a family, age of lymphoid cancer onset, subtype of lymphoma, genetic sharing amongst affected individuals in a family, variant population frequency and in silico predictions of the variant’s function. Once scored, variants and genes from all the lymphoid cancer families are combined to provide a prioritized list of variants and genes which will be investigated further. Validation of these variants and genes will be performed on the remaining families and individuals. Identifying genes and variants that contribute to susceptibility to lymphoid cancers will allow a better understanding of the biological processes underlying familial lymphoid cancers and may lead to new insights for prevention of these cancers.
30. PATIENT SELECTION FOR A DEVELOPMENTAL THERAPEUTICS PROGRAM USING MULTI-OMICS

Lavoie J.-M. 1*, Mitchell T. 1, Lee S.-E. 1, Deol B. 1, Jones S.J.M. 2, Marra M. 2, Laskin J. 1, RENOUF D.J. 1

1BC Cancer – Vancouver Centre, Vancouver Canada; 2Michael Smith Genome Sciences Centre, Vancouver Canada. * Presenting author is a trainee (postgraduate fellow).

Category: Translational/Clinical

Introduction: Given the high level of uncertainty surrounding the outcomes of early phase clinical trials, Whole Genome and Transcriptome Analysis (WGTA) can be used to optimize patient selection and study assignment. In this retrospective analysis, we review the impact of this approach on one such program.

Methods: Patients with advanced malignancy underwent fresh tumour biopsies as part of our personalized medicine program (NCT02155621). Single nucleotide variants, structural variants, copy number alterations, RNA expression, tumor mutational burden (TMB) and mutational signatures were derived from WGTA. Each case was reviewed for potential actionable genomic events (AGEs) in a multidisciplinary tumor board. Selected patients were referred to the developmental therapeutics program; an AGE was not required for enrollment provided they met inclusion criteria for each individual study.

Results: From January 2014 to January 2018, 28 patients underwent WGTA and enrolled in clinical trials, including 2 patients enrolled in two trials. AGEs were found in 18 cases and used in half (15/30) of cases for treatment allocation. Findings were derived from single-gene DNA changes in 6 cases, RNA expression in 10 cases and whole genome analysis (for mutational signatures or TMB) in 6 cases. All single-gene DNA changes were supported by RNA expression. Results are presented after a median follow-up of 59 weeks.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>AGE-based (n=15)</th>
<th>Not AGE-based (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecular targeted agent</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Checkpoint inhibitor</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Antibody-drug conjugate</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Best Overall Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Median time on treatment (weeks)</td>
<td>8.3</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Discussion: WGTA can provide key information to facilitate treatment assignment in developmental therapeutics, especially for small molecular targeted agents with a clear mechanism of action. Using only genomic data derived from single-gene DNA changes would have captured less than half of AGEs, thus emphasizing the role of multi-omics in this setting.
31. OUTCOMES AND CHARACTERISTICS OF PATIENTS RECEIVING SECOND-LINE THERAPY FOR ADVANCED PANCREATIC CANCER


Erica Tsang is a PGY-4 Medical Oncology trainee.

Category: Translational/Clinical

Background: Recent trials have demonstrated improved outcomes in the 1st-line treatment of advanced pancreatic cancer (APC). However, there is limited randomized data to guide 2nd-line chemotherapy (CT) selection. We aimed to characterize predictors and outcomes of 2nd-line CT in patients (pts) with APC.

Methods: We identified all pts with APC (locally advanced (LAPC) or metastatic (MPC)) who received ≥1 cycle of 1st-line CT between January 1, 2012 and December 31, 2015 across 6 centers in British Columbia, Canada. Baseline characteristics and survival outcomes were summarized.

Results: Of 676 pts with APC (31% LAPC, 69% MPC) who received ≥1 cycle of CT, 164 (24%) received 2nd-line CT. These pts were younger (median 63.7 vs. 67.4 years; \( p =0.01 \)), had a lower ECOG (77% ECOG 0-1 vs. 51% ECOG ≥2; \( p<0.001 \)), and higher CA19-9 (median 1034 vs. 829; \( p=0.01 \)) compared to patients who did not receive 2nd-line CT. There were no differences in rates of 2nd-line CT between LAPC and MPC (28% vs. 23%; \( p=0.18 \)). On logistic regression, only 1st-line FOLFIRINOX (OR 5.90, \( p<0.001 \)) was associated with 2nd line CT. CT regimens are summarized by line (Table). Median duration of 2nd-line CT was 3 cycles (range 1-30).

Median overall survival (mOS) from diagnosis of patients with 2nd-line CT was 16 months. mOS from 2nd-line CT was longer with 2nd-line gemcitabine/nab-paclitaxel than fluoropyrimidinide or gemcitabine (7.9 vs. 5.1 vs. 4.3 months; \( p=0.008 \)). On multivariate analysis, longer OS from 2nd-line CT was associated with gemcitabine/nab-paclitaxel (vs. single agent CT), lower ECOG, LAPC (vs MPC), and lower CA 19-9 (HRs 0.49, 0.67, 0.58, 0.38, respectively).

Conclusion: In this population-based cohort, pts treated with 2nd line CT were younger, have better ECOG, similar rates of LAPC vs. MPC, and achieved a median OS of 16 months. 1st-line FOLFIRINOX was the strongest predictor of 2nd-line CT. Gemcitabine/nab-paclitaxel was associated with superior 2nd line OS compared to gemcitabine/fluoropyrimidinide.

Table. Regimens used in pts who received 2nd-line CT

<table>
<thead>
<tr>
<th>1st-line CT</th>
<th>2nd-line CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRINOX</td>
<td>109 (67%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>31 (19%)</td>
</tr>
<tr>
<td>Gemcitabine/nab-paclitaxel</td>
<td>23 (14%)</td>
</tr>
<tr>
<td>Fluoropyrimidine</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4 (2%)</td>
</tr>
<tr>
<td></td>
<td>74 (45%)</td>
</tr>
<tr>
<td></td>
<td>33 (20%)</td>
</tr>
<tr>
<td></td>
<td>44 (27%)</td>
</tr>
<tr>
<td></td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>
32. MULTIPLEXED DIGITAL SPATIAL IMMUNE PROFILING REVEALS A SUBSET OF BREAST CANCER PATIENTS WITH FAVORABLE PROGNOSIS

Burugu S.¹ (PhD Candidate), Liang Y.², Gong J.², Hinerfeld D.², and Nielsen T.O.¹

¹UBC Department of Pathology and Laboratory Medicine; ²Nanostring Technologies, Seattle

Category: Biology/Informatics

Background: Immunotherapy is dramatically changing the cancer treatment landscape. Recent clinical trials of immune checkpoint inhibitors are reporting promising results in a subset of metastatic breast cancer patients with the aggressive basal-like subtype. Biomarkers of response to immune checkpoint inhibitors are the center of intensive research. Anti-tumor immunity is mainly mediated by T cells, which represent a heterogeneous population. In addition, other immune cells play key roles in anti-tumor immunity. The concurrent infiltration of the various immune cell populations in a patient’s tumor may impede or improve responses to immunotherapies. Nonetheless, to analyze multiple immune biomarkers concurrently in a patient’s tumor tissue represents a technical challenge. In this study, we used a novel quantitative spatially-resolved multiplexed immunohistochemistry method called digital spatial profiling (DSP) using NanoString’s GeoMx™ technology. This method allows for simultaneous quantitative measurement of multiple biomarkers on formalin-fixed paraffin-embedded tumor tissues.

Material and methods: Based on antibodies linked to UV-cleavable oligonucleotides that are quantified on the NanoString nCounter® platform, we analyzed the spatially distinct expression of 31 protein biomarkers, part of an immuno-oncology validated panel, in breast cancer tissue microarrays consisting of two cohorts (39 patients in cohort A and 20 patients in cohort B). All patients in cohort B were of basal-like breast cancer subtype whereas this subtype represented 40% of the cases in cohort A. Clinicopathological and outcome data were available for the cohort A. In addition, hematoxylin and eosin-stained stromal tumor infiltrating lymphocytes (H&E sTILs) scores were available for all patients.

Results: Immune biomarker expression counts were interpretable in 37 out 39 cases from cohort A and in all 20 cases for cohort B. Unsupervised hierarchical clustering of the immune biomarker expression counts categorized patients from cohort A into 4 major groups (G): G4 (n=14), G3 (n=11), G1 (n=6) and G2 (n=6). Patients clustering in G2 and G3 had immune-enriched breast tumors, whereas patients in G1 and G4 had little to no lymphocytes infiltration in their tumors. CD20 and PD-1 protein expression appear to discriminate between patients in G2 and G3 wherein, G2 had the highest counts for CD20 and PD-1 expression. More than half of the breast cancer patients in the G2/G3 were of the basal-like subtype. Furthermore, G2/G3 were significantly associated with moderate (≥10%) to high (>50%) sTILs levels as observed on H&E sections, providing a visual validation of the digital spatial profiler’s results. In survival analyses, breast cancer patients in G2/G3 had significantly improved survival in comparison to patients G1 and G4 (Log rank p=0.013). In cohort B (where all patients were basal-like), there was only a minority of tumors (n=5/20) that had little to no immune infiltration. In contrast, the majority of cohort B patients clustered into 2 groups that had moderate to high immune infiltration, again correlating significantly with H&E sTIL counts.

Conclusion: Using DSP, we identified a subset of patients with immune-enriched breast cancers associated with a favorable prognosis. This technology has the potential to evaluate the immune context of non-responding vs responding tumors to immunotherapies.
33. CLINICAL BENEFIT OF WHOLE GENOME AND TRANSCRIPTOME ANALYSIS (WGTA) IN METASTATIC COLORECTAL CANCER (MCRC): RESULTS FROM THE PERSONALIZED ONCOGENOMICS PROGRAM (POG)

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Category: Translational/Clinical

Background: Standard guidelines recommend mutation testing for KRAS, NRAS and BRAF in MCRC. POG at BC Cancer is an investigational project that performs WGTA to identify potential hypothetical actionable biomarkers. We aimed to determine its clinical significance compared to standard sequencing panels by analyzing the prevalence of actionable variants and their impact on treatment decisions.

Methods: We analyzed 69 POG MCRC patients (pts) and summarized their WGTA results to identify germline and somatic coding variants, copy number alterations, structural alterations and gene expression outliers. Actionable items were defined as variants that could direct therapy with an investigational or approved agent, and were classified as either standard (found in local sequencing panel- BC Oncopanel) or expanded (not in current sequencing panel).

Results: 74% of pts received 2 or more prior lines of chemotherapy. 1 pt died before biopsy was made available and 1 pt had an unsuccessful biopsy. Remaining analysis of 67 pts revealed 49 (73%) pts with actionable alterations, of which 43% consisted of mutation changes, 40% expression changes, 14% copy number variants, and 3% high mutational burden or HRD. Most common standard alterations (54%) were mutations in TP53, KRAS, BRAF, PIK3CA and most common expanded items (46%) were high expression of FGFR1/3, FLT1/3, and VEGFA/B. Among these, 13 (27%) pts had alterations that led to standard chemotherapy or anti-EGFR based treatment, and 7 (14%) pts had a variant that resulted in non-standard therapies. Of those, only irbesartan, targeting the FOS-JUN pathway, resulted in a meaningful response duration of 28 months, while the remaining had an average PFS of 1.7 month. 29 (59%) pts did not receive therapy outlined in POG analysis due to lack of access for the target drug (n=15), poor performance status (n=7), and patient or physician preference (n=7).

Conclusion: WGTA in MCRC provided additional understanding of tumor biology, with high rates of expression changes not otherwise captured in standard sequencing panel. However, at the present time, there is limited additional therapeutic benefit in comparison. A major contributor to the low rate of enrollment in clinical trial is due to lack of access to drugs. Future development is needed and ongoing.
34. EOSINOPHILS IN THE LUNG TUMOR MICROENVIRONMENT

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Category: Biology/Informatics

Background: The use of immunotherapy to treat lung cancer is becoming increasingly common, highlighting the importance of the immune system in the lung tumor microenvironment. The lungs are host to a variety of immune cell subsets, including eosinophils (Eo), which are a population of innate immune cells that exert cytotoxic effector functions through the release of secretory granules and participate in tissue homeostasis and immunity. Despite the presence of Eo in solid tumors and their prevalence in the lung, the role of Eo in lung cancer is both controversial and largely unexplored. The Bennewith lab has previously found that mice with elevated lung Eo have decreased tumor growth in a model of breast cancer lung metastasis. We hypothesize that Eo play a protective role in lung cancer growth.

Methods: In collaboration with Dr. Kelly McNagny (UBC), we used IL-5Tg transgenic mice that over-express IL-5 and have a systemic expansion of Eo, ddGATA transgenic mice which are Eo-deficient, and ddGATA/IL-5Tg double-transgenic mice (excess IL-5 but no Eo) to study lung cancer. Lewis Lung carcinoma (LLC) cells were injected intravenously (IV) to seed the lungs. After three weeks, we harvested lungs and used flow cytometry to quantify lung immune cell subsets. Additionally, we used clonogenic assays and histology to quantify lung tumor growth.

Results: We confirmed that naive ddGATA and ddGATA/IL-5Tg mice have no lung Eo. In contrast, IL-5Tg mice have a 100-fold expansion of Eo in the lungs, and these Eo express higher levels of the Eo activation marker CD11b compared to wild-type (WT) mice. Naive IL-5Tg and ddGATA/IL-5Tg mice had an increased proportion of lung B-1 B cells, as well as an increase in the expression of the apoptosis-inducing cell surface molecule FasL. The absence of Eo in ddGATA mice did not impact lung colonization of LLC cells. Though there was a substantial expansion of Eo in the lungs of IL-5Tg mice compared to WT mice, there was no change in the number of lung-infiltrating Eo three weeks after IL-5Tg and WT mice were injected IV with LLC cells. IL-5Tg mice injected IV with LLC cells had an increase in the total number of lung-infiltrating B_{conv} and B-1 B cells compared to naive mice, whereas there was no change in B cell subsets between naive and LLC IV injected WT mice.

Conclusions: Though Eo may play an anti-tumorigenic role in the presence of excess IL-5, the absence of Eo in ddGATA mice did not result in an increase in lung tumor burden. This suggests that Eo need to be activated and expanded to exert an anti-tumorigenic effect, or that the expansion of B cells in IL-5Tg mice is responsible for the decrease in lung tumor growth in IL-5Tg mice relative to WT mice. Though immunotherapies have improved lung cancer treatment responses, most of these therapies target cells of the adaptive immune system, therefore combining these therapies with therapeutics that target innate immune cells could drastically improve patient outcomes. Illuminating the specific roles Eo and B cells play in lung cancer progression will allow us to better understand the interplay between host immune cells and malignant cells and could reveal new avenues of cancer immunotherapy development.
35. LOSS OF MIR-146A LINKS INFLAMMAGING WITH MYELOID MALIGNANCY


*Post-doctoral fellow

Category: Biology/Informatics

Background: Hematopoietic stem cells (HSCs) are specialized bone marrow cells capable of differentiation to produce all mature blood cell types and self-renewal to maintain the HSC pool. Both chronic inflammation and aging impair HSC function, with strikingly similar effects on HSC self-renewal, propensity toward myeloid differentiation, and cell cycle quiescence. Chronic low-grade inflammation in the absence of infection, or sterile inflammation, is a hallmark of aging termed “inflamming”. Thus, it is possible that HSC aging occurs by a process of inflamming, but mechanisms driving increased sterile inflammation of aging remain poorly understood. Defects in HSC function also underlie many hematological malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Intriguingly, inflammation is also a common feature of MDS and AML, raising the possibility that common mechanisms driving inflammation may occur in HSC aging and leukemic transformation. In this study, we present evidence that loss of the MDS- and AML-associated microRNA \textit{miR-146a} is a common mechanism linking inflammation, HSC aging, and leukemic transformation.

Results: Previous research has shown that loss of \textit{miR-146a} is sufficient to cause features of MDS or AML in mouse models; however, the effect of \textit{miR-146a} loss on HSC function prior to the onset of overt malignancy remains poorly characterized. In the present study, we found that loss of \textit{miR-146a} in mice expands the immunophenotypic HSC pool but severely reduces the frequency of functional, serially transplantable HSCs. Using single-cell resolution analyses of HSC quiescence, stemness, differentiation potential, and epigenetic state, we identified multiple characteristics suggestive of premature HSC aging in young \textit{miR-146a} null mice. Intriguingly, \textit{miR146a} expression decreased significantly in HSCs isolated from aged wild type animals, suggesting that loss of \textit{miR146a} may be a driver of normal HSC aging. HSC aging in \textit{miR-146a} null mice coincided with low-grade sterile inflammation, a hallmark of inflamming. Transcriptome profiling of \textit{miR-146a} hematopoietic stem and progenitor cells identified interleukin 6 (IL6) and tumor necrosis factor (TNF) signaling as potential drivers of HSC inflamming. Reducing inflammation mediated by IL6 or TNF restored HSC function in young \textit{miR-146a} null mice, and delayed the onset of MDS- or AML-like disease in aging \textit{miR-146a} null mice. Importantly, we observed enhanced IL6 and TNF signaling-activated gene expression in human AML with reduced expression of \textit{miR-146a}, suggesting a conserved mechanism in human myeloid malignancy with loss of \textit{miR-146a}.

Conclusion: Overall, our results suggested that loss of \textit{miR-146a} links HSC inflamming with the development of myeloid malignancy. Our findings provide direct evidence that inhibiting inflammation not only restores HSC function, but also reduces the predisposition to developing myeloid malignancy.

This work is supported by a TFRI PPG Grant (#1074).
**36. DISTRACTED DRIVING? AN EXAMINATION OF CONSOLE INTERRUPTIONS DURING RADIATION THERAPY TREATMENT**

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*Category: Population Health/Health Services*

**Introduction:** The risks associated with workplace distractions are well documented. Distracted working can lead to an increase in workplace injuries and errors. Errors in radiation therapy treatment delivery by radiation therapists (RTTs) are relatively rare, but when they do occur can lead to serious consequences. In the radiation therapy environment distractions can stem from interruptions during treatment, for example by co-workers, patients and other sources. The problem of distraction in radiation therapy departments during treatment has not been well examined. Focused attention by RTTs is particularly important during the time that the treatment machine is delivering a beam of radiation. Inattention due to distraction or interruptions can result in errors, for example, a mismatch between patient set up information and the identity of the patient on the treatment couch or targeting errors due to unexpected patient movement. This study quantifies the amount and types of treatment interruptions found in three BC Cancer centres.

**Methods:** A non-participant observation study of the types of distractions occurring during treatment was carried out using a standard checklist plus field notes (e.g. to capture an unusual interruption). The process and tool were piloted before use.

**Results:** Of 94 treatments observed, 51 experienced interruptions (54%). Thirty two were interruptions by RTTs (either team members or RTTs from different units), 15 were from a patient or family, seven were from another healthcare professional, seven were “other” and four were phone calls. Field notes indicate that console area design and patient flow can impact on the amount and types of interruptions.

**Conclusion:** It is hoped that data capturing the typical distraction events, and how often these occur, will lead to measures to improve the working environment of RTTs at BC Cancer.
37. EMOTIONAL DISTRESS AND PSYCHOSOCIAL NEEDS IN PATIENTS WITH BREAST CANCER: YOUNGER VS. OLDER ADULTS


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Category: Population Health/Health Services

Purpose: Depression and anxiety are common among patients diagnosed with breast cancer. As part of a province-wide psychosocial screening program, BC Cancer patients complete the PsychoSocial Scan for CANcer – Revised (PSSCAN-R) questionnaire, which screens for risk of anxiety and depression and assesses patient-reported psychosocial needs using the Canadian Problem Checklist (CPC). The purpose of this study was to evaluate the prevalence of emotional distress in young adult (YA, age 18-39) patients at the time of their cancer diagnosis as compared to older patients. We also examined how the specific psychosocial needs differed between these age groups.

Patients and Methods: The study population was comprised of all breast cancer patients who completed the questionnaire within 6 months of their cancer diagnosis between 2011-2016. Clinical information was retrospectively collected from electronic health records. Univariate analysis using the $X^2$, Fisher’s exact test and logistical regression were used to compare patient age groups.

Results: The cohort included 10,734 breast cancer patients; median age 62, 4% YA, 99% female and 96% presented with non-metastatic disease. Compared to older breast cancer patients, YA patients were more likely to report depression (33.6% vs. 25.5%, OR 1.48, $p<0.0001$) and anxiety (58.6% vs. 35.7%, OR 2.54, $p<0.0001$). YA patients were more likely to report needs within emotional (OR 2.63, $p<0.0001$), informational (OR 1.70, $p<0.0001$), practical (OR 2.50, $p<0.0001$), spiritual (OR 1.43, $p=0.002$) and social (OR 1.89, $p<0.0001$) domains on the CPC. Specifically, needs regarding work/school (OR 3.79, $p<0.0001$), intimacy/sexuality (OR 2.82, $p<0.0001$) and finances (OR 2.78, $p<0.0001$) were much more common among younger vs. older adults.

Conclusion: After a breast cancer diagnosis, YAs have significantly higher levels of emotional distress compared to older patients. Differences in specific psychosocial needs likely reflect differences in the values between these age groups. The data suggests that YAs warrant specific attention with respect to early psychosocial assessment and tailored intervention.
38. ONCOGENES DRIVE PRODUCTION OF IMMUNOSUPPRESSIVE CYTOKINES TO FACILITATE LUNG CANCER PROGRESSION

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Category: Biology/Informatics

Lung cancer development is driven by the expression of mutant oncogenes, with EGFR and KRAS being the most frequent mutations in lung adenocarcinoma. However, these mutations alone are not sufficient for tumorigenesis and additional factors influence tumor development and progression, including the balance of anti-tumor immune effector cells and pro-tumorigenic immune suppressor cells within the tumor environment. We hypothesized that oncogene signaling regulates the production of cytokines by tumor cells in order to modulate the immune microenvironment and promote lung tumor development. We used CIBERSORT to quantify 22 immune cells cell types in over 300 human lung adenocarcinomas (LUAD) and 100 matched normal lung tissues. Cells associated with inflammatory or anti-tumour response, macrophages (M1, M0), T follicular helper cells, and plasma cells were enriched in LUAD compared to normal lung tissue. Additionally, immunosuppressive regulatory T cells (Tregs) were significantly enriched in early stage LUAD tumors. To identify cytokines that could be induced by oncogenic signaling early in lung tumorigenesis, we used normal cells expressing doxycycline inducible mutant KRASG12V mutant EGFRL858R or wild-type EGFR and analyzed cytokine production with a multiplex assay (LUMINEX). Induction of oncogenic signaling in normal cells rapidly increased production of cytokines CCL5 and CCL2. These are capable of recruiting a variety of cell types, including Tregs. In KRAS mutant lung cancer cells, disruption of oncogene signaling with a MEK inhibitor (Trametinib) decreased CCL5 production. We used transgenic mice that spontaneously develop lung tumors in response to tetracycline-inducible expression of mutant EGFRDelEx19 or mutant KRASG12V in type II alveolar cells to investigate immune cell populations that may change in response to oncogene driven lung tumorigenesis. We found that Tregs were increased in the lungs of tumour bearing mice. These Tregs express the CCL5 receptor, CCR5. Several cytokines were elevated in bronchoalveolar lavage fluid or in lung lysates of tumor bearing mice, including IL-12(p40), CXCL1, CCL2, CCL3 and CCL5. Murine Lewis lung carcinoma (LLC) cells harbor a KRAS mutation and express high levels of CCL5. We are currently investigating the effects of disrupting oncogene signaling or CCL5 expression in LLC cells on cytokine production and immune cell recruitment in vivo using syngeneic implantation of the cells into mice. Our data suggest that oncogenic signaling regulates expression of cytokines in lung tumor cells. Targeted inhibition cytokines or oncogenic signaling may represent therapeutic strategies to block the recruitment of immune suppressive cells to the tumor microenvironment, thereby enhancing the anti-tumour immune response.
39. IMPACT OF EXERCISE ON CHEMOTHERAPY COMPLETION RATES IN INDIVIDUALS WITH CANCER: A SYSTEMATIC REVIEW

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Category: Biology/Informatics

We completed a systematic review to evaluate the influence of exercise interventions on chemotherapy completion rate outcomes in adult cancer patients. Relevant literature was retrieved from CINAHL, Medline (Ovid), and EMBASE based on subject headings and keywords pertaining to cancer, exercise, and chemotherapy. Title, abstract, and full-text screening was performed using Covidence. Articles included in this review were randomized or single-arm studies with a comparison group, prescribed aerobic or strength training, and included endpoints relating to chemotherapy completion rates. Chemotherapy completion rates were evaluated in 7 randomized and 2 single-arm trials. No study measured chemotherapy completion rates as the primary outcome. Chemotherapy completion rate definitions included mean/median relative dose intensity (RDI) or RDI ≥ 85% (n=4), planned minimum/maximum cycles and chemotherapy response (n=1), rate of chemotherapy interruption (n=1), % participants requiring dose adjustment/mean dose adjustment/receipt of planned dose (n=1), time to start chemotherapy cycle 2 (n=1), and dose intensity (n=1). Overall, 2 RCTs and 2 single-arm trials reported significant beneficial effects of exercise on chemotherapy completion rates, including mean RDI ranging from 90-95% with exercise vs. 80-84% without exercise. The remaining 5 studies showed no difference by group. Despite a growing literature of exercise oncology trials conducted to-date, few have evaluated the exercise’s effect on chemotherapy completion rates. Given the prognostic importance of receiving the planned chemotherapy dose/duration, designing exercise trials to evaluate chemotherapy completion rates as a primary outcome is needed.
40. MALIGNANT PLEURAL MESOTHELIOMA TISSUE-OF-ORIGIN CLASSIFIERS DEVELOPED FROM NOVEL MIRNAS SEQUENCES

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Category: Translational/Clinical

Diagnosis and tissue-of-origin identification of malignant pleural mesothelioma (MPM) is currently assessed using a panel of positive/negative markers; however, there remains a subset of cases that are not definitively identified.

The key role of miRNAs in cancer biology has encouraged their evaluation as clinical markers. Recent evidence indicates that the human genome encodes more miRNAs than are currently annotated, most of them displaying tissue-specific patterns. Here, we hypothesized that MPM tumors express a specific set of previously-uncharacterized miRNA sequences, and these species can distinguish MPM from other thoracic diseases.

We conducted a *de novo* search for novel miRNAs sequences in a cohort of MPM tumors (n=87), using smallRNA sequencing data from The Cancer Genome Atlas (TCGA). Using the newly-identified miRNA species, we performed a genomewide 3’UTR target prediction analysis using the miRanda algorithm. To investigate the ability of novel miRNAs to distinguish MPM from other thoracic cancers, we assessed their expression in 1,093 lung tumors from four independent sample cohorts from TCGA and the BC Cancer Agency (BCCA): two adenocarcinoma (LUAD) cohorts (TCGA n=497, BCCA n=94) and two squamous cell carcinoma (LUSC) cohorts (TCGA n=467, BCCA n=35). Finally, a classifier model was built using the weighted voting class prediction method.

We identified 424 predicted novel miRNA-like sequences, which were subsequently filtered by RNA structure, abundance, and genomic location to identify a high-confidence set of 154 previously unannotated miRNA sequences. Some of the most highly expressed novel miRNAs were predicted to establish thermodynamically stable interactions (based on sequence homology) with 3’UTR region of genes relevant to MPM biology, such as the Ataxia Telangietasia Mutated (ATM) and BRCA1 Associated Protein 1 gene (BAP1).

A principal component analysis revealed that combined expression of the 154 newly-discovered miRNAs unambiguously distinguished MPM from LUAD and LUSC. To explore their clinical potential, we developed a 10-novel miRNA classifier by comparing MPM and LUAD cases from TCGA and validated by comparing MPM against LUAD cases from the BCCA cohort. Remarkably, this classifier successfully identified 86 out of the 87 MPM cases (98.8%) and 100% of LUAD cases (true positive rate = 98.85%, false positive rate = 1.15%).

Here, we provide evidence for the presence of 154 previously unidentified miRNA species in MPM. These miRNAs not only significantly expand the miRNA repertoire but also unveil specific roles in MPM biology. Furthermore, the specificity of these novel miRNAs could supplement current clinical practices and help to address unmet clinical needs in MPM.
YOUNG-ONSET COLORECTAL CANCER: A WORLDWIDE SYSTEMATIC REVIEW OF POPULATION STUDIES OF INCIDENCE

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Presenting author is a graduate student under the supervision of Dr. Mary De Vera.

Category: Population Health/Health Services

Background/Purpose: Recent data suggest that the risk of young-onset colorectal cancer (yCRC) is increasing. To identify the consistency of these findings and identify trends, our objective was to conduct a systematic review of the literature examining population-level incidence and prevalence of yCRC.

Methods: We conducted a systematic search of MEDLINE (1946-2018), EMBASE (1974-2018), CINAHL (1982-2018), and Cochrane Database of Systematic Reviews (2005-2018) using a combination of database-specific subject terms and keywords for concepts of “colorectal cancer”, “young onset/young-adult”, and “epidemiology”. Inclusion criteria were: 1) original research study using epidemiologic design; 2) reporting estimates of incidence and/or prevalence of yCRC (or enough information to calculate); and 3) published in English. We extracted data on country, datasource, date range, cancer site (e.g. CRC, rectal cancer [RC]), age, and sample size and critically appraised studies using two previously reported tools.

Results: Our search strategy resulted in 1,804 articles. Among 46 included studies, none reported prevalence. 27 studies were from the Americas, 14 from Asia, 3 from Africa, 1 from Europe and 1 worldwide. Reported incidence rates for yCRC ranged from 0.42 per 10\textsuperscript{5} in 2010 in the US to 13.7 per 10\textsuperscript{5} in 2016 in Australia. With respect to trends, annual percent changes in the incidence (APCi) of yCRC overall ranged from +1.03 (95% confidence interval [CI], 0.985, 1.088) from 2001 to 2008 in New South Wales Australia to +3.0 (95% CI, 0.7, 5.5) from 1982 to 2007 in Western Australia. Among subgroups, particularly, ethnicity and we extracted the highest APCi's for African Americans (+22.8 (95% CI, 21.2, 24.5) and Asians/Pacific Islanders +18.0 (95% CI, 16.9, 19.1) from 1988 to 2009 in the US.

Conclusion: Findings of our systematic review showing an increasing risk of yCRC overall and according to reported sub-groups provide support to a paradigm shift in CRC and the importance of raising awareness of the impact of the disease in younger adults.
42. MATCHING METHODS IN PRECISION ONCOLOGY: AN INTRODUCTION AND EXAMPLE

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Category: Population Health/Health Services

Background: Randomized controlled trials (RCT) are uncommon in precision oncology. In the absence of RCTs, quasi-experimental matching methods are increasingly used to estimate the health impacts of omics-guided care. We provide an introduction and illustrative example of matching in precision oncology.

Methods: Our case study focuses on the British Columbia Personalized OncoGenomics (POG) program, which applies whole-genome and transcriptome analysis (WGTA) to identify targeted treatments for patients with advanced cancers. Our cohort comprises patients who participated in POG between July 2014 and December 2015 and matched POG-naïve controls. We generated our matched cohort using retrospective administrative data in combination with 1:1 propensity score matching (PSM) and genetic matching. After matching, we estimated Kaplan-Meier survival functions and Weibull regression models to explore the survival benefits of POG.

Results: During our study period, 230 patients participated in POG and 5,224 control patients were eligible for matching. Final matched cohorts each included 230 POG-naïve controls after weighting. Genetic matching outperformed PSM when achieving balance on covariates of interest. Survival analyses on unmatched and matched cohorts indicated that overall survival did not significantly differ across POG and control patients (p>0.05). Stratification by WGTA-informed treatment revealed differences in estimated survival. In all cohorts patients whose WGTA information led to treatment change were at a statistically significantly reduced hazard of death compared to controls. Estimated hazard ratios ranged from 0.33 (95% CI: 0.13, 0.81) in propensity score matched patients, to 0.34 (95% CI: 0.14, 0.86) in genetic matched patients, to 0.41 (95% CI: 0.17, 0.98) in unmatched patients.

Conclusions: Matching methods combined with population-based administrative data offer a solution to the challenges of non-randomized enrollment observed in many applications of precision oncology. Yet validity of these methods relies on strong underlying assumptions. Careful study design and balance assessment are critical to ensure reliable effect estimates.

The authors have no conflicts of interest to declare.
OUTCOMES OF STEREOTACTIC BODY RADIOTHERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Category: Translational/Clinical

Background: Stereotactic body radiotherapy (SBRT) is an emerging curative treatment for hepatocellular carcinoma (HCC). We report toxicity and efficacy of all patients treated in British Columbia, one of the largest series to date.

Methods: From 2011 to Jan 2018, 99 patients underwent SBRT to 128 HCCs. Fiducials were placed and 4D CT (78.4%) and respiratory gating (19.6%) were used for motion management. Local control (LC), progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier. Cox regression identified outcome predictors.

Results: Median Child-Pugh Score (CPS) was A5 (65% A5, 18% A6, 12% B7, 5% B8, 1% B9) and median Albumin-Bilirubin (ALBI) score was -2.55, grade 2 (48% gr1, 45% gr2, 6% gr3). Most (87.7%) had either Hepatitis B or C and 73.7% had prior HCC treatment, with 47.5% going on to further HCC treatment post SBRT and 42.4% deceased at the time of analysis. The median tumor size was 2.8 cm (range 0.8 – 11). The median prescribed biologically effective dose (BED10) was 112.5 Gy, with 45 Gy in 3 fractions (BED10 112.5 Gy) in 56.9% of cases and 45 Gy in 5 fractions (BED10 85.5 Gy) in 30.4%. Median follow-up was 18.5 months (range 2.2 – 73.5). At 3 months, 12 (11.8%) patients had a rise in CPS of ≥ 2, and 26 (25.5%) patients had increased ALBI grade (median change in score of +0.16). Excluding laboratory findings, 14 (14.1%) patients developed CTCAE V5 grade 3 / 4 toxicities (ascites n=12, hepatic failure n=4, hepatic pain n=1, nausea n=1, GI bleed n=1). The 1-, 2- and 3-year LC were 94.3%, 86.6% and 80.2%. The median PFS was 14.8 months, respectively 53.7%, 39.5% and 23.8% at 1, 2 and 3 years. The median OS was 41.1 months, respectively 80.3%, 63.5% and 55.2% at 1, 2 and 3 years. Univariate factors predicting improved LC were mean dose (Dmean) ≥ BED10 100 Gy to GTV (p<0.01) and PTV (p=0.03). Predictors of improved OS were prescription dose ≥ BED10 100 Gy (p=0.02), GTV Dmean ≥ BED10 100 Gy (p<0.01), lower CPS (p=0.04) and lower ALBI score pre-SBRT (p<0.01), smaller tumor size (p<0.01), no liver directed therapy post-SBRT (p<0.01), younger age (p=0.03) and favorable ECOG (p=0.01).

Conclusions: SBRT achieves excellent LC, with low rates of toxicity and can be included with or without other therapies in HCC treatment.

Disclosures: None for all authors.
Purpose: To evaluate the dose calculation accuracy of the Varian Eclipse anisotropic analytical algorithm (AAA) for stereotactic ablative body radiotherapy (SABR) in comparison with Monte Carlo (MC) in order to investigate the dosimetric consequences to organs at risk (OAR) and coverage of planning target volume (PTV) in lung SABR plans.

Materials and Methods: 25 cases of non–small-cell lung cancer (NSCLC) that were previously treated with SABR to 48 Gy in 4 fractions at our center were selected for this study. These cases were treated from March 2016 to February 2018 and were selected such that the PTV size covers a wide range, from 8.9 cc to 163.2 cc. IGTV was contoured from the 4DCT and a 5 mm isotropic expansion was applied to form PTV. The original treatment plans were calculated with 6FFF beams using AAA in Eclipse Treatment Planning System. The same plans were recalculated using MC for the purpose of this study. DVH data has been exported for all cases and later processed using in-house developed R scripts. The following dose-volume parameters were used for the comparison: V100%, V90% and Dmin to the PTV; conformity index (V100%/VPTV), low dose conformity (V50%/VPTV) and D2cm; V100% to IGTV; V20Gy for the lung; dose parameters to OARs including chest wall, esophagus, great vessels, brachial plexus, trachea, heart, bronchial tree, skin and cord. The statistical comparison has been done by paired t-test analysis.

Results: Comparable results were obtained for AAA and MC calculations except for V100% to the PTV (p < 0.001), conformity index (p = 0.008), low dose conformity (p < 0.001) and lung V20Gy (p < 0.001). The largest difference was observed for V100% to PTV which in turn impacts the conformity index too. AAA calculations underestimated dose to lungs and PTV compared to MC. The dose differences in PTV Dmin and PTV V90% as well as D2cm were not statistically significant. No correlation has been observed between the PTV size and the dose differences between AAA and MC. Occasionally, MC revealed hot and cold spots which were not present in the AAA calculations.

Conclusions: Our results demonstrate that AAA and MC doses to OARs are in good agreement most of the time with the exception of the lung. In terms of PTV coverage, AAA underestimates V100% to PTV. Based on our investigation, AAA is a good choice for routine planning but for the purpose of plan-specific QA, employing the MC algorithm or equivalent, e.g., Acuros is the appropriate thing to do. Further investigations are necessary in larger patient cohorts to determine whether AAA is still appropriate for dose calculation of lung SABR plans if cases where the field sizes are very small.
PATIENT-REPORTED PERSONAL FINANCIAL IMPACTS FOLLOWING TREATMENT FOR RARE BLOOD CANCERS: A LONGITUDINAL STUDY

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* Presenting author is a trainee.

Category: Population Health/Health Services

Objective: The study objective was to assess and compare patient-reported financial impacts following treatment of newly diagnosed acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS); two rare and serious forms of blood cancer. AML has acute progression, requiring intensive treatment and long hospital admissions, whereas MDS treatments are less intense and the disease progression is typically more chronic in nature.

Methods: We administered societal cost questionnaires to participants in the Terry Fox Research Institute’s observational clinical study (NCT01685619) at: baseline, 3, 6, 12, 18 and 24 months. The key exploratory endpoints were baseline-to-3 and 6 month changes in measurements of personal financial impacts including: lost income and employment, out-of-pocket expenses related to drugs or medical visits (i.e. transportation and accommodation). Productivity impacts were captured by the transition from full or part-time work to unemployment and short-term or long-term disability insurance. The significance of the differences in out-of-pocket expenses and productivity between patients with AML versus MDS was investigated with Wilcoxon rank-sum (Mann-Whitney) tests.

Results: A total of 138 patients completed the baseline societal cost questionnaire. Response rates were between 50% to 71% across all time points. Over the first six months of treatment, AML patients on average lost more personal income than patients with MDS; the average monthly lost income was $1786.41 for AML patients vs. $608.15 for MDS at 3 months and $1660.89 vs. $636.57 at 6 months (p<0.05). The total monthly out-of-pocket expenditure for AML patients was also higher compared to MDS patients over the first three months of treatment; $559.14 for AML patients vs. $239.14 for MDS patients (p=0.051). Lost productivity and non-reimbursed prescription drugs are two main factors that drive up the increased personal financial impacts for AML patients. The majority of AML patients (57%) who were working full-time, and younger than 60 years of age at baseline, did not return to work after 24 months.

Conclusions: AML patients report significantly worse personal financial outcomes compared with patients with MDS and other cancer patients, indicating disparity in this patient group.

This study was funded by the Terry Fox Research Institute.
Introduction: The study objective was to evaluate practice adherence to the upfront management of differentiated thyroid cancer (DTC) in accordance with the ATA guidelines and the impact on outcomes.

Methods: BC Cancer provides cancer care for over 4.5 million Canadians. A retrospective review of DTC patients referred to BC Cancer between 2009 and 2013 was conducted. Baseline characteristics, upfront surgical management, adjuvant radioactive iodine (RAI) and external beam radiotherapy (XRT) were evaluated. Disease management was assessed for adherence with the 2009 ATA guidelines. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared with the log rank test.

Results / Discussion: 1095 DTC patients were referred to BC Cancer (~65% of all diagnoses of DTC in the province). Baseline characteristics: female 73%, median age 50, histology; papillary 90%, follicular 7%, Hurthle cell 3%. Stage at presentation using the AJCC 7th edition was: I 58%, II 8%, III 21%, IVA/B 11%, IVC 2%. Surgical management for multifocal disease and/or cancer > 1 cm was: lobectomy 3%, total thyroidectomy 69%, and staged total thyroidectomy 28%. Lymph node sampling was performed for tumors > 4 cm in 62%. RAI was delivered in 83% of patients with tumors > 4 cm, M1 disease and/or gross extrathyroidal extension. Curative intent XRT was utilized in 48% with T4 lesions. The 5 year outcomes for management consistent with guideline recommended primary surgery and/or nodal management versus non-adherence was DFS 78% versus 75% (p>0.05), and OS 94% versus 92% (p>0.05). The 5 year outcomes for guideline recommended adjuvant RAI +/- XRT versus non-adherence was DFS 79% versus 40% (p<0.001), and OS 95% versus 61% (p<0.001).

Conclusions: In our population-based cohort, compliance with ATA guideline recommended surgical management did not affect the DFS or OS. The DFS and OS were significantly inferior if patients did not receive the recommended adjuvant RAI +/- XRT. RAI and XRT are integral components of the management of DTC and should be utilized within the context of ATA guideline treatment recommendations.

A POPULATION-BASED REVIEW OF SALVAGE SURGERY, RADIOACTIVE IODINE, EXTERNAL BEAM RADIATION, AND SYSTEMIC THERAPY FOR MANAGEMENT OF RECURRENT DIFFERENTIATED THYROID CANCER

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Category: Biology/Informatics

Introduction: Management of recurrent differentiated thyroid cancer (DTC) may include surgery, radioactive iodine (RAI) and/or external beam radiotherapy (XRT). Patients may also be treated with systemic agents such as sorafenib and lenvatinib for RAI refractory DTC. The study objective was to evaluate DTC recurrent disease treatment and utilization of systemic therapy.

Methods: BC Cancer provides cancer care for over 4.5 million Canadians. A retrospective review of all DTC patients referred to BC Cancer between 2009 and 2013 was conducted. Baseline characteristics, local/distant recurrence, surgical management, RAI, external beam radiotherapy (XRT), and systemic therapy details were collected. Disease free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results / Discussion: 1066 DTC patients were referred to BC Cancer with stage I-IVB disease (~65% of all diagnoses in the province). Median follow-up 4.1 y. Baseline characteristics: female 74%, median age 50 y, histology; papillary 92%, follicular 5%, Hurthle cell 3%. Stage at presentation using the AJCC 7th edition: I 60%, II 8%, III 21%, IVA/IVB 11%. Local and/or distant recurrence occurred in 141 patients (13%). 122 (11%) of the patients with local recurrence were treated with primary surgery +/- RAI or XRT 50%, RAI +/- XRT 42%, XRT alone 1%, untreated 7%. 33 (3%) had a second recurrence and were treated with primary surgery +/- RAI or XRT 40%, RAI +/- XRT 24%, XRT alone 3%, other 3%, and untreated 30%. Of 39 patients who developed distant metastatic disease, 20 had prior local recurrence. Common sites of metastases were lung 72%, bone 28% and liver 8%. Of the entire cohort, 6 (0.6%) received systemic therapy with sorafenib. The 5 y DFS was 80% and OS was 95% for all patients.

Conclusions: In our population-based cohort, 87% of patients were cured by primary disease management. Local recurrence was successfully managed with surgery, RAI and/or XRT with no evidence of residual disease in 65% of patients. Multi-modality treatment of local recurrence facilitates complete disease ablation in the majority of patients, and despite a significant number of metastatic recurrences, only a small fraction of patients require systemic therapy.

Background: Socioeconomic status (SES) and geographic factors may impact patient treatment choices. Canada has a publically funded health care system and in BC, there are 35 community oncology network sites that delivery treatment in patients’ local communities. We studied the impact between SES and geographic location upon delivery of chemotherapy/survival in metastatic NSCLC.

Methods: All patients with metastatic NSCLC referred to BC Cancer centres from 2011-2015, who completed a prospective Canadian Problem Checklist questionnaire at the time of their first visit and for which chemotherapy data was available were included in the study. The CPC assesses patient distress in 6 domains including practical aspects of cancer care. The Postal Code Conversion File Plus uses data from Statistics Canada 2011 census to determine population size and income quintiles. Baseline characteristics and chemotherapy treatments were collected retrospectively. Univariate analysis using the Chi-squared test and Fisher’s exact test were used for analysis.

Results: 2224 patients were included with median age of 69 years, 50% male and 81% were former/current smoker and 47% received palliative chemotherapy. Uptake of chemotherapy did not differ between lowest+mid-lowest 39%, middle 43% /mid-highest+highest 44% income quintiles (p=0.1). Chemotherapy use was also similar between patients reporting financial concerns 42% versus none 41% (p=0.73). Uptake of chemotherapy was lower in patients who lived in rural communities population<10 000 39%, 10K-1.5M 37%, >1.5 million 46% (p<0.001). Chemotherapy use was lower for patients with concerns about getting to appointments (37% vs 42%, p=0.028) or accommodations (33% vs 42%, p=0.002).

Conclusion: This dataset provide evidence that patients from rural communities were less likely to receive palliative chemotherapy treatment for metastatic NSCLC in BC despite the availability of multiple local community oncology services. SES did not appear to impact the proportion of patients treated, congruent with a government funded health care system. An in depth assessment of distances to local cancer services and treatment delivery is warranted to investigate these differences and their effect on mortality.
49. BRINGING THE VOICE OF PRIMARY CARE TO BC CANCER: RESULTS FROM A PROVINCE-WIDE PRIMARY CARE ONCOLOGY NEEDS ASSESSMENT FOR PROGRAM PLANNING

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Category: Population Health/Health Services

Background: The Family Practice Oncology Network (FPON) was established in 2002 as a means to enhance family physicians’ abilities to provide cancer care, including the administration of systemic therapy and supportive care, in rural communities. FPON has evolved to offer continuing medical education (CME) programming and cancer care practice tools to support family physicians. In 2017, with a 40% increase in cancer diagnoses projected by 2030, BC Cancer has committed to provide significantly more support to family physicians through more effective integration of primary care into the continuum of cancer care and the work of BC Cancer. The Provincial Primary Care Program (evolution of FPON) was established, a Provincial Lead appointed, and efforts began to determine the focus and direction of this enhanced support network.

Methods: In 2017, FPON and its long-time CME partner, the University of British Columbia’s Division of Continuing Professional Development (UBC CPD), undertook a formal needs assessment to determine how to best strengthen family physicians’ and primary care providers’ ability to care for cancer patients. The development of the needs assessment was led by a working group with representation from FPON, UBC CPD and family practice. Questions focused on the following key topic areas: roles and care delivery, clinical knowledge, communication, the role of BC cancer and educational needs.

The needs assessment was conducted in three phases with results from each phase informing the next. This included nine key informant interviews, a comprehensive online survey distributed to approximately 5000 family physicians in BC and the Yukon in addition to nurse practitioners and registered nurses, followed by four focus groups (new to practice family physicians, rural family physicians, urban family physicians, and oncologists) to gain insight into identified priorities.

Results: The top three priorities identified for the Provincial Primary Care Program are to: advocate for improved access to clinical resources/services for patients; develop primary care practice tools to support patients with cancer; and provide oncology education and training for primary care physicians. The four areas in which to develop strategies include: information resources, educational programming, communication practices, and relationship building.

Conclusions: The results of this province-wide needs assessment will guide the development of BC Cancer’s recently established Provincial Primary Care Program (an expansion of FPON) and inform BC Cancer’s current and future interactions with the primary care system.
50. GENOMIC ANALYSIS OF TUMOUR-IMMUNE LANDSCAPE AND DETERMINANTS OF RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN PERSONALIZED ONCOGENOMICS PATIENTS

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Category: Translational/Clinical

Background/Purpose: Immune checkpoint inhibitors are revolutionary cancer immunotherapy drugs that target immune checkpoints (e.g. PD-1, PD-L1, and CTLA-4), thus invigorating T cells to attack tumour cells. Since their emergence in 2011, immune checkpoint inhibitors are now widely prescribed for diverse cancer indications. However, there is high variability in how individual patients respond. Therefore, this project addresses the urgent need to better understand tumour-immune dynamics in order to identify more robust biomarkers of response to immune checkpoint inhibitors.

Methods: We analyzed whole genome sequencing, whole transcriptome sequencing, and clinical data of 570 patients with diverse metastatic cancers (of which 84 have received immune checkpoint inhibitors) in the BC Cancer POG (Personalized OncoGenomics) cohort using bioinformatics techniques including cell type deconvolution, T cell repertoire analysis, and SNV-based neoantigen prediction.

Results: Across 26 cancer types in the POG cohort, we characterized the composition of tumour-infiltrating immune cells, T cell clonotype repertoire, predicted tumour neoantigens, and expression of tumour-associated antigens. We also demonstrated the utility of these metrics in predicting time to treatment failure on immune checkpoint inhibitor therapy.

Conclusions: Our results support the role of tumour antigens in shaping the tumour immunome in diverse metastatic cancers, and investigate new determinants of response to immune checkpoint inhibitors. These findings have the potential to guide more effective use of immune checkpoint inhibitors in the clinic.

No conflicts of interest.
51. THE CARA PILOT STUDY: A NOVEL BREAST SUPPORT TO REDUCE TOXICITY IN ADJUVANT WHOLE BREAST RADIOThERAPY IN SUPINE POSITION

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Category: Translational/Clinical

Purpose: A novel Carbon-fibre Adjustable Reuseable Accessory (the CARA) breast support for adjuvant whole breast radiotherapy was designed and fabricated at BC Cancer, Vancouver. The device is designed to reduce skin reactions and volume of normal tissue (including heart and lung) irradiated without interfering with treatment. Feasibility testing has established evidence that the CARA has the potential to reduce treatment toxicity for many breast cancer patients. The pilot study will establish safety, clinical workflow, measured skin dose and patient reported outcomes using the CARA during treatment, in preparation for a randomized clinical trial.

Materials and methods: A feasibility study was performed on 10 patients (5 left breast) undergoing CT simulation, treatment planning and set-up for whole breast radiation treatment with the CARA and without CARA. Eligibility criteria included brassiere size of D cup or greater or having infra-mammary skin fold > 1 cm. Left and right breast patients were included in this study. Deep inspiration breath-hold technique was used for left breast patients. Portal imaging was performed to assess setup reproducibility. Treatment planning data included infra-mammary skin fold depth, tangential field length, volume of body receiving 50% or more and 105% or more of the prescription dose, volume of heart receiving 25Gy or more, volume of ipsilateral lung receiving 20Gy or more, monitor units, treatment setup time, and setup shifts required to achieve an acceptable treatment position. The same eligibility criteria and procedures were then applied in the design of a treatment pilot study. A total of twenty patients will be recruited to the treatment pilot currently underway. Patients will receive the full course of whole breast radiotherapy treatment using the CARA. In-vivo skin dose is measured during 3 treatment fractions using radio-chromic film placed in contact with the breast skin. Patient reported outcomes are collected using the POSI B-Skip questionnaire on skin toxicity. All six BC Cancer centres are invited to recruit patients to this study.

Results: The CARA breast support setup requires an average of less than 2 minutes. No collisions with radiotherapy equipment were encountered and no image artefacts were observed with the CARA in place. In all 10 feasibility study cases heart V25Gy ≤ 5% constraint was met and heart V25Gy was maintained within 1% with CARA versus without; the lung V20Gy ≤ 35% constraint was met in all cases and lung V20Gy was improved in 7/10 cases with CARA. 7/10 cases had reduced field length with CARA (up to 3.5 cm reduction); reduced MU’s were observed with CARA in 8/10 cases and reduced 10 MV versus 6 MV weighting was observed in 5/10 cases with CARA.

Conclusion: These promising results provide the motivation for a full clinical trial to assess reduction in toxicity achievable using this novel breast support.

This work is supported by the Canadian Cancer Society through a 2018 Innovation to Impact Grant # 705797; BC Cancer US Patent No. 62/464941.
INCRNAS EXPRESSED FROM PSEUDOGENE LOCI ARE DEREGULATED IN LUNG ADENOCARCINOMA


Category: Biology/Informatics

The advent of next generation sequencing has begun to reveal the functional importance of long non-coding RNAs (lncRNAs) in human cell biology, which can be exploited by tumours to drive the hallmarks of cancer. As such, lncRNAs deregulated in cancer may represent critical members of cancer pathways that could hold therapeutic applicability. Due to their complex tertiary structure there is a growing disparity between number of lncRNAs identified and those that have been functionally characterized, and there is a need to identify downstream targets. Pseudogenes are non-coding DNA sequences that are defunct relatives of their protein-coding parent genes but retain high sequence homology. Interestingly, several lncRNAs expressed from pseudogene loci have been shown to regulate the protein-coding parent genes of these pseudogenes through sequence complementarity. We hypothesize that this phenomenon occurs more broadly than previously realized, and that aberrant expression of lncRNAs overlapping pseudogene loci provides an alternative mechanism of cancer gene deregulation.

Illumina HiSeq reads were processed and aligned to the ENSEMBL annotation. Two datasets were selected due to their paired nature, complete with both lung adenocarcinoma (LUAD) and non-malignant lung profiles (TCGA n=108, BCCA n=72). LncRNAs were filtered based on positional overlap within pseudogene loci. Differential expression was identified by Wilcoxon sign-rank test (FDR p<0.05). To identify lncRNAs that likely regulate protein-coding parent gene expression in trans, tumours were ranked by lncRNA expression, and protein-coding parent gene expression of top and bottom ranked tertiles was compared by Mann Whitney U-test (p<0.05). Survival analysis was performed using a Cox proportional hazard model.

Our analysis identified lncRNAs expressed from pseudogene loci that were significantly deregulated in LUAD in both datasets. Remarkably, many of these deregulated lncRNAs (i) were expressed from the loci of pseudogenes related to known cancer genes, (ii) had expression that significantly correlated with protein-coding parent gene expression, and (iii) protein-coding parent gene expression was significantly associated with survival. Implying that these lncRNAs deregulated in LUAD may function through controlling the expression of these cancer, and patient survival associated parent genes. This work uncovers evidence to suggest the lncRNA-pseudogene-protein-coding gene axis is a prominent mechanism of cancer gene regulation.
53. ROBUST PICKET FENCE QUANTIFICATION

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Category: Biology/Informatics

Multileaf collimator (MLC) leaf position accuracy is crucial during radiotherapy since small leaf position offsets can result in large dosimetric errors for patients. Picket fences are a QA procedure used to assess leaf position accuracy. Use of monthly picket fence QA is specifically recommended in the latest Canadian Partnership for Quality Radiotherapy (CPQR) technical quality control guidelines, and a tolerance of 0.5mm is recommended. However, quantifying picket fences is challenging due to changes in calibration, the wide variety of possible dose profiles across leaf gaps, stray pixels, and geometrical variance across linacs.

Recently, while commissioning a new linac with refined leaf gap control, the picket fence dose profile was found to exhibit significant peak-trough variability. Existing open source analysis tools were unable to quantify the gap and we were left unable to assess leaf position accuracy. To remediate this clinical issue, we created a novel non-parametric analysis algorithm that can handle arbitrary peak-trough shapes, stray pixels, and detector-MLC rotation. It quantifies leaf gap separations using a statistically robust procedure based on multi-sampling of the gap dose profile and does not require open-field or baseline measurements.

An implementation of the algorithm suitable for analyzing DICOM RTIMAGE picket fences was validated using an intentionally-bad picket fence and found to be sensitive to leaf position errors <0.25mm. Sensitivity to detector-MLC rotations is high and appears to be limited by the width of a single detector pixel. Three years of historical picket fences were analyzed retrospectively to characterize individual machines; we found that the age of the linac correlates with the magnitude of detector-MLC rotation correction needed, leaf gap tends to grow over time, and leaf position variations seem to coincide with MLC interventions.

In this work we give an overview of our algorithm, describe results of our historical investigation, and demonstrate how to use the web application.
54. VALIDATION OF A RADIOMIC FEATURE EXTRACTION MODULE IN DICOMAUTOMATON

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Category: Biology/Informatics

Introduction: Radiomics is an emerging field of research that has potential to directly impact the clinical practice of radiotherapy[1,2]. Radiomic features can be implemented in a variety of ways, differing for example by shifts or scales, and implementation differences can also impact repeatability[3]. The International Biomarkers Standardization Initiative (IBSI) was created to establish a unified description of radiomic features and provide benchmarks for validation[4].

A radiomics module was implemented using the open source DICOMautomaton software platform. DICOMautomaton provides a compelling base for a radiomics extraction tool since it was designed to quantify images and radiotherapy dose metrics. In particular, radiomic evaluation can be conveniently integrated into an automated clinical workflow via DICOMautomaton.

In this work we validate the DICOMautomaton radiomic feature extraction module against the IBSI benchmarks for a non-small-cell lung carcinoma patient CT data set[5], IBSI feature definitions, and the reported consensus-derived benchmarks.

Methods and Materials: A subset of 22 radiomic features defined by the IBSI that are consistently found to be strong factors in radiotherapy applications were implemented. DICOMautomaton uses ROI contours directly rather than converting to bitmap masks. While this has advantages for ROI demarcation and resolution-independent adaptive resampling, the definition of some IBSI features were modified or simplified to suit.

The IBSI corpus comprises image sets from four patients. Features were compared using a Wilcoxon’s sign test with α=0.05.

Results: The value of individual features differed from the IBSI consensus benchmarks by no more than 0.75%. The two-tailed Wilcoxon sign test for all paired features resulted in a z-statistic of -0.7113 and p > 0.45, implying there is no significant difference between the IBSI and DICOMautomaton feature definitions or implementations.

Conclusions: The radiomic feature extraction module integrated into the open source DICOMautomaton software platform conforms to IBSI radiomics benchmarks.

References
Background: Intravenous infusion pumps with medication safety software such as Dose Error Reduction Software (DERS) can reduce the risks associated with intravenous (IV) administration. DERS pump technology incorporates safeguards within a drug library to help improve patient safety and decrease medication errors. It also captures infusion data to allow for evaluation of pump use pattern and opportunities for improvement. A Continuous Quality Improvement (CQI) review utilizing pump data was conducted at the BC Cancer with the objective of evaluating frequency of alerts, analyzing incidence and root causes to provide recommendations for systems changes to improve safety, prevent alert fatigue and standardize practice.

Methods: Data was collected from Alaris® Guardrails CQI Reporter, pharmacy and electronic patient chart databases. Paclitaxel, oxaliplatin and fluorouracil were selected for review since they have been identified as the top three drugs causing alerts each month. Infusion concentration, duration, dose and excess volume were the parameters analyzed, as they are the most common alerts identified in CQI reporting. The results were then reviewed by an interdisciplinary committee to link data to practice.

Results: There was a high incidence of paclitaxel, oxaliplatin and fluorouracil alerts (>70%) observed. The underlying causes for the alerts included underestimation of IV bag overfill volume calculation, mismatch between concentration calculation in chemotherapy protocols and practice and non-standardized fluorouracil administration protocols. As a result of the review, plans are in place to streamline and update practices and protocols.

Conclusion: CQI analysis of Smart pump data provides a simple, measurable, achievable, reportable tool for evaluating pump use patterns. Using an interdisciplinary review approach, data are reviewed in a practical, meaningful way to shape practice and reduce risk for medication errors.
The BC Cancer Registry is a population-based database that tracks information on newly diagnosed cases of cancer and cancer deaths in the province of British Columbia (BC). The Registry contains a diverse array of data on demographics, residential location, diagnosis, stage at diagnosis, and mortality information that can support a wide range of data users. Potential users include researchers monitoring trends in cancer incidence, mortality or survival, or using the Registry for cancer information for studies aimed at identifying causes and preventability of cancer. The data also support a significant number of other stakeholders including medical health officers who may require data to respond to community or “cancer cluster” concerns, health planners who may require long term projections of future cancer burden for capital planning and the public who may want information about cancer in their community.

This diverse array of stakeholders requiring aggregated or summarized data using different disease measures and dimensions (e.g. age, sex, cancer type, location) and the increasing demands for up to date cancer information have motivated the development of an interactive informatics tool that enables end user generation of cancer information. Our presentation will introduce the Cancer Incidence and Mortality Dashboard, a self-service tool that enables analysis and visualization of cancer incidence and mortality information from the provincial BC Cancer Registry using the software Tableau. Users can generate cancer incidence and mortality counts, crude rates, age-standardized rates and standardized incidence and mortality ratios. Users are able to drill down and filter on a variety of dimensions, such as age, sex, geographic area (health authority, health service delivery area and local health area), cancer type as well as select the date range (currently 1986 to 2015) of interest. Summaries from the tool can also be exported for further analysis in statistical software packages enabling further epidemiological analyses such join-point regression or age-period-cohort analyses.

This poster will review the motivation for such a project, describe the design approach to the tool, display screenshots of the current dashboard and its functionality and discuss current and future access/implementation plans. We will also propose some research uses for the tool including epidemiologic analyses or obtaining information on new cancers relevant for planning a trial or prospective study.
57. ORAL LICHENOID DYSPLASIA - AT RISK OF MALIGNANT PROGRESSION

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Category: Translational/Clinical

Objectives: Oral lichen planus (OLP), a chronic mucocutaneous inflammatory condition, is recognized as potentially malignant by the World Health Organization. However, this designation is heavily debated in the literature. Some argue that only OLP with epithelial dysplasia – referred to as lichenoid dysplasia (LD) – have malignant potential. Others postulate that the architectural and cellular changes seen in LD is not indicative of true dysplastic change, but rather part of the reactive and inflammatory process occurring in OLP. In this study, we investigated the risk of malignant transformation of LD by comparing the proportion of malignant progression of LD with that of oral epithelial dysplasia (OED) without lichenoid features.

Methods: Clinical data was collected from the Oral Cancer Prediction Longitudinal (OCPL) study. Patients with a histologically confirmed mild or moderate OED or LD and no history of head and neck cancer were examined and followed at 6-month intervals (n=446). Demographic, risk habit, clinicopathological, and histologic data were collected. The outcome of interest was progression to severe dysplasia, carcinoma-in-situ, or squamous cell carcinoma. Categorical variables were tested using the Chi-square test or Fisher’s exact test. Quantitative variables were tested using independent samples t test or Mann-Whitney U test. The threshold for significance was set at P<0.05, and all tests were two-tailed.

Results: Out of 446 subjects, 55 (12%) progressed to endpoint. There was no significant difference in progression between LD and OED. Rather, progression was significantly associated with non-smoking (P=0.03), location at a high-risk site (floor of the mouth or tongue) (P<0.001), and the severity of dysplasia (P=0.003). A diagnosis of moderate LD or OED had a higher likelihood of progression (OR 2.34; 95% CI 1.31 – 4.18; P=0.003) compared to those with a mild diagnosis.

Conclusions: LD and OED possess a similar risk of malignant transformation. Therefore, any dysplasia seen in LD should not be discounted as reactive, but instead should be followed and biopsied at regular intervals.

Acknowledgements: This work was supported by grants from the British Columbia Cancer Foundation. L.R. is the recipient of a CIHR Doctoral Research Award (379723) I.L. is the recipient of a University of British Columbia Faculty of Dentistry Summer Research Studentship.

Keywords: Oral lichen planus, oral epithelial dysplasia, malignant progression, mouth neoplasms

Conflict of Interest: None.
PROGNOSIS AFTER LOCO-REGIONAL FAILURE OF BREAST CANCER: 34 YEARS OF LONGITUDINAL DATA FROM THE STOCKHOLM CANCER REGISTER


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Background: Survival after loco-regional failure (LRF) of breast cancer was investigated at the population level.

Methods: Using the Stockholm cancer registry, 2698 patients diagnosed with LRF between 1980 and 2014 were identified and divided into three cohorts by year of LRF diagnosis. Post-relapse event-free survival (EFS) and overall survival (OS) were analyzed separately in local and loco-regional relapses and compared across the cohorts by Kaplan–Meier method. Relative survival was estimated and Poisson regression models, adjusted for clinically relevant prognostic factors, were fitted for excess mortality ratio calculation. Age-related survival trends were also explored.

Results: Among 1922 patients diagnosed with local relapse, 1032 (54%) EFS events and 931 (48%) deaths were registered. A significant improvement in EFSS (p<0.001) and OS (p<0.001) was demonstrated in tumors that recurred locally in the years 1990–1999 and 2000–2014 compared with 1980–1989, regardless of age at relapse (≤60 years; >60 years). In women with loco-regional relapse, 557 out of 776 (72%) experienced a post-relapse event and 522 (67%) died. Significantly longer EFS and OS were seen over time in the whole group (p<0.001 and p=0.003, respectively) and in younger (p<0.001; p<0.001) but not in older women (p=0.55; p=0.80). Relative survival was consistent with OS and a statistically significant decrease in mortality after loco-regional recurrence over time was seen only in women aged ≤60 years.

Conclusions: Survival after loco-regional failure of breast cancer has improved over time, especially in younger women.

This study was supported by the Swedish Cancer Society (CAN 2015/713), the Cancer Society in Stockholm (154132), Breast Cancer Theme Center (BRECT) at Karolinska Institutet, and the Stockholm County Council.
59. DETECTION OF 134C>W FOXL2 MUTANT EXPRESSION AND QUANTIFICATION BY ISOBARIC DOPING

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Category: Translational/Clinical

Adult Granulosa cell tumors (aGCTs) are a sub-type of ovarian cancer that constitutes 2-5% of ovarian tumours. Previously a heterozygous 134C>W pathognomic mutation in FOXL2 was identified in 97% of the patient aGCT samples analyzed. ChIP-Seq was used to identify about a dozen genes that exhibited both a change in their ChIP-Seq peaks and an increase in mRNA expression for the mutant FOXL2. To verify these data at the protein level, mass spectrometry (MS)-based proteomics analysis of aGCTs was performed using the quantitative single-pot solid-phase-enhanced sample preparation-Clinical Tissue Proteomics (SP3-CTP) protocol. In brief, peptides obtained from trypsin digested proteins were labeled with Tandem Mass Tags (TMTs), and MS was performed to quantify protein expression in cells. However, the majority of targets were not reproducibly detected at the protein level. When peptide sampling by MS is performed in an abundance-dependent manner, it may result in irreproducible or no detection of low abundance peptides, such as those generated from transcription factors or having somatic mutations.

To drive reproducible detection of low abundance peptides from proteins of interest, we implemented quantitative isobaric peptide doping (isodoping) for a set of proteins and mutations of interest. These proteins and mutations were selected based on the ChIP-Seq data, global proteomics data, and the literature. For proteins with either less than five peptides consistently detected per protein, or if the protein was not detected at all, up to five unique proteotypic peptides were selected for each protein to be used as isodoping peptides. This scheme increases the chance of detecting 3 or more peptides per protein to increase the confidence of protein inference. In total, 286 peptides for 74 target proteins were synthesized and analyzed as a library by MS. Of the 286 peptides in the library, 218 were detected at 200 fmol on column, corresponding to 94% of the proteins detected by 3 or more unique peptides. The reasons that not all peptides were detected by MS could be poor MS characteristics, poor synthesis, and inaccurate concentrations. To rescue the missing peptides, the undetected isodoping peptides were pooled and analyzed separately; 12 of 68 initially undetected peptides were detected in this separate analysis, indicating that these peptides were either at too low a concentration or obscured by the other peptides in the mixture. The 68 originally undetected peptides were spiked back into the original pool at 2x, 5x, or 10x the original concentration and analyzed. 230 peptides (72 proteins) were detected in the 2x concentration, while 223 peptides (70 proteins) were detected in 5x, 218 peptides (69 proteins) in 10x. Due to the stochastic sampling of the instrument, these three detection numbers are approximately the same and the 2x concentration was selected for further experiments. Ongoing work is directed toward determining the amount of peptide required to spike into a TMT-plex for reliable detection of target peptides in SVOG (granulosa) and KGN (aGCT) cell lysates and this method will eventually be applied to aGCTs to quantify the presence of mutated FOXL2. The method will be useful for the analysis of somatically mutated proteins in general.
60. ACCORDION-LIKE MODEL OF H3K27ME3 EXPANSION AND CONTRACTION DURING HEMATOPOIETIC LINEAGE COMMITMENT

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TFRI Research Project Title: Exploiting Pathogenic Mechanisms in Acute Leukemia

Category: Translational/Clinical

Introduction: Hematopoiesis describes the process of blood cell formation and development. The critical step of hematopoiesis, HSCs commitment to lineage-restricted progenitors, is regulated by network of transcription factors and epigenetic modifications. Here, we are presenting a comprehensive whole genome map of transcription and epigenetic modifications that are representative of active and suppressed chromatin. We subsequently examine the dynamics of these modifications at different stages of hematopoiesis.

Methods: Chromatin immunoprecipitation sequencing (ChIP-seq) targeting histone3 lysine 4 trimethylation (H3K4me3), H3K4me1, H3K27me3, H3K27ac, H3K36me3, and H3K9me3 was conducted on aliquots of 10,000 progenitor cells from a pool of CD34+ cord blood cells (CD34+; CD38−, Common myeloid progenitors CD7−; CD34+; CD38+; CD10−; CD45RA−; CD135+, Granulocyte myeloid progenitors CD7−; CD34+; CD38+; CD10−; CD45RA+; CD135+, Myeloid Erythroid progenitors CD7−; CD34+; CD38+; CD10−; CD45RA−; CD135−), Erythroid Progenitors (CD45−; GPA+) and Monocytes/Macrophages (CD45+; CD34−; CD33+; CD11b+; CD14+). The resulting data were integrated with matched RNA-seq and whole genome bisulfite sequencing datasets.

Results: Comparisons of the H3K27me3, a repressive histone modification, landscape across hematopoietic populations revealed a stable polycomb signature among progenitor cells, in contrast to active histone modifications signature such as H3K4me3 and H3K27ac. Progenitor cell’s H3K27me3 landscape shows genome wide rearrangement at the late stages of differentiation. H3K27me3 landscape in differentiated myeloid cells undergoes contraction genome wide and resembles the H3K27me3 phenotype in embryonic cells. This contraction of polycomb signature in differentiated cells is accompanied by a loss of large organized H3K27me3 domains (LOCKs) that are present in progenitor populations. In contrast to myeloid cells, differentiated lymphoid cells (B-cells and T-cells) do not show the same contraction of H3K27me3 upon differentiation. In addition, primary acute myeloid leukemic cells and HL60 cell line did not share the H3K27me3 phenotype of myeloid differentiated cells. Furthermore, inhibition of H3K27me3 lysine demethylases prevents the commitment of CD34+CD38− to myeloid lineage. These results portray the importance of chromatin structure and organization of H3K27me3 in hematopoietic differentiation.

Conclusions: Our results support a model where accordion-like expansion and contraction of H3K27me3 play a role in regulating lineage commitment and differentiation.
61.  **PLOIDTECT: INTERPRETABLE DETECTION OF TUMOR CONTENT AND ANEUPLOIDY FROM WHOLE GENOME SEQUENCE DATA**

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**Category: Translational/Clinical**

**Introduction:** Whole-Genome Sequencing (WGS) of tumors is being increasingly adopted to inform clinical decision-making in the treatment of cancer. Two notable obstacles in analysis of tumor sequence data are estimation of tumor purity and detection of aneuploidy. We present Ploidetect, a statistical framework which simultaneously estimates tumor purity and ploidy from WGS data. Ploidetect is robust to a large degree of tumor heterogeneity and provides accurate estimates of extremely impure tumors.

**Results:** Ploidetect was applied to a cancer cohort comprising of previously treated metastatic tumor WGS data (n = 710). For each sample, tumor content and ploidy estimates were independently calculated by a team of expert bioinformaticians using standard bioinformatics pipelines. We found good concordance between Ploidetect estimates and manual review (Pearson's r = 0.88). Ploidetect estimates fell within 10% of the manual review assessment in 74% of cases. Re-analysis of 40 discordant (|Ploidetect - manual review| > 20%) estimates demonstrated that Ploidetect provided more accurate estimates in 75% of the assessed cases. Furthermore, Ploidetect provided more accurate estimates compared to other existing tools in a set of test cases (n=8). Copy number alternation calling with the method demonstrated promising results and is an area of further work.

**Discussion:** Ploidetect is demonstrably superior to existing methods for estimation of tumor purity, including manual review. The results obtained from Ploidetect are simple to assess for accuracy by a human reviewer. Improvement of copy number alteration calling is an area for further improvement.

**Methods:** WGS data are summarized as read counts within fixed-width bins across the genome. Read counts within bins are next normalized for mappability errors and gaussian kernel density estimation is used to call peaks of abundant read count states. We model the normalized read counts within each bin as a linear combination of reads originating from tumor and contaminating normal DNA. We generate models describing tumor purity and evaluate their fit to the observed data. Ploidy is determined using observed single nucleotide polymorphism frequencies across the genome as well as read count data.
Introduction: Fetal and tumour development share striking similarities, such as intense cell proliferation, angiogenesis, increased cell motility, and immune evasion. Consequently, investigation of lung tumour biology in the context of lung development may reveal key regulatory mechanisms that tumours hijack from normal development.

Methods: 131 pairs of non-small cell lung cancer (NSCLC) tumour and non-malignant lung tissues and 5 human fetal lung tissue samples were profiled by miRNA-sequencing. To investigate protein-coding genes controlled by the oncofetal miRNAs identified, miRDIP was applied followed by luciferase-reporter assays. Associations between patient survival and mRNA expression of selected oncofetal miRNA-gene targets were evaluated in ~1,400 NSCLC cases. Immunohistochemical analysis of oncofetal miRNA targets was performed on a lung adenocarcinoma (LUAD) tissue microarray.

Results: We describe for the first time a comprehensive characterization of miRNA expression in human fetal lung tissue, and identified numerous miRNAs that recapitulate their fetal expression patterns in NSCLC. Nuclear Factor I/B (NFIB), a transcription factor essential for lung development, was identified as being frequently targeted by these oncofetal miRNAs. Concordantly, analysis of NFIB expression in multiple NSCLC cohorts revealed its frequent underexpression in tumours (>60%). Remarkably, low expression of NFIB was significantly associated with higher grade, biologically more aggressive subtypes of LUAD, and ultimately, poorer survival in LUAD patients.

Conclusions: This work reasserted the commonalities between the processes regulating normal lung development and lung tumourigenesis, and, for the first time, in terms of a comprehensive characterization of miRNA expression patterns. Our analyses revealed a prominent mechanism for the downregulation of NFIB through oncofetal miRNAs, and suggest that NFIB may serve as a useful biomarker for LUADs with poor prognosis. Restoration of NFIB expression in LUAD may induce lung cell differentiation, and therefore has the potential to reduce tumour aggressiveness.
63. EVALUATION OF $^{18}$F-EF5 SUITABILITY FOR DETECTION OF HYPOXIA IN LOCALIZED ADENOCARCINOMA OF THE PROSTATE

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BJW is a PhD Candidate.

Category: Biology/Informatics

Introduction: A common feature of therapy resistant and metastatically aggressive solid tumours is the presence of regions with low oxygen content (i.e. hypoxia). Oxygen electrode studies suggest that localized prostate adenocarcinoma are commonly hypoxic, although conflicting data has been reported between IHC detection of endogenous hypoxia markers and PET scans of both $^{18}$F-FMISO and $^{18}$F-FAZA hypoxia reporters. It remains unclear if 2-nitroimidazoles are not suited to detection of prostate tumour hypoxia, or if there is a limitation in the hypoxia-specific uptake of $^{18}$F-FAZA or $^{18}$F-FMISO. $^{18}$F-EF5 is an alternative 2-nitroimidazole with promising results in models of prostate cancer as well as clinical trials of other primary tumours, the purpose of this study was to evaluate $^{18}$F-EF5 for its suitability to detect hypoxia in localized prostate adenocarcinoma.

Methods: Prostate cancer patients were recruited from BC Cancer for pre-treatment $^{18}$F-EF5 PET imaging along with biopsy collection for IHC analysis of glucose transporter 1 (GLUT1) expression to check for hypoxic status. GLUT1 expression was scored by a pathologist for staining intensity and frequency.

Results: This study was halted after eight patients were recruited and no significant $^{18}$F-EF5 uptake could be detected in any tumours. However, significant GLUT1 expression was observed in 4/8 tumours. Two of the cases were scored as strongly positive for GLUT1 with high frequency (>50% tumour positive), while the other two positive cases were scored as positive with moderate frequency (<50% tumour positive). This is fitting with intra- and inter-individual heterogeney reported in oxygen electrode analyses of clinical prostate tumour hypoxia.

Conclusions: These data do not support the use of $^{18}$F-EF5 in localised prostate adenocarcinoma. Our study agrees with the observations made with $^{18}$F-FAZA where no radiotracer uptake was detected despite some cases of positive IHC staining for hypoxia induced proteins.
Over the last year there has been significant work underway to standardise best practice in chemotherapy scheduling. This includes the time that the nursing team is allocated per protocol (the Chemotherapy Data Dictionary), and how appointments are scheduled in order to optimize efficiency (through a decision-support tool known as Chemo Smartbook).

The Chemotherapy Data Dictionary for Systemic Therapy Treatment is an up to date file that contains all active protocols and the corresponding nurse and chair times. This was created through using a methodology developed by Cancer Care Ontario, and follows an algorithm for determining the appropriate nurse and chair time for each protocol.

Chemotherapy patient scheduling is considered to be a very challenging task due to the large differences between protocols and the associated variation in resource requirements, treatment time, complexity and cost as defined in the chemotherapy data dictionary. Chemo Smartbook is a scheduling optimization tool that makes use of high-level prescriptive analytics technique known as constraint programming. It relies on a pre-determined set of goals/objectives and restrictions/constraints to book chemotherapy patients with various protocols and requirements for treatment. The outputted daily treatment schedule seeks to maximize resource utilization, meet patient appointment time preferences and balance the workload across a variety of available resources (pharmacy/rooms/chairs/nurses) while adhering to all constraints, such as resource availability and standard operating procedures. This tool is being updated to connect with Cerner and to have enhanced scheduling features while making use of best practice guidelines to organize nursing workload and workflows to fit expected patient needs.

This poster will review the journey that both of these projects have taken, including the goals and purpose of these tools, and how they connect. We will also review the methodology for assessment, clinical validation and outcome measures of success of this translation from research to clinical practice, along with the sustainment and change management required for it to be successful.
DECISION MAKING IN PROVINCIAL SYSTEMIC THERAPY

ANDERSON H., Nakashima L., Clyne-Salley S.

Category: Translational/Clinical

BC Cancer Provincial Systemic Program is responsible for the introduction and management of Cancer drugs within the Province – including the 6 Cancer Centre’s and 42 Community Oncology Network Sites.

The rapid pace of cancer drug development, coupled with finite health budgets and human resources has necessitated the evolution of both the National and Provincial frameworks by which decisions are made, and development of a more co-ordinated approach to understanding the resources needed to deliver systemic treatment safely and efficiently.

Within this poster, we will share the updated framework for how drugs are assessed and reviewed (including the collaboration with National organizations and Provincial partners), along with preliminary findings and evaluation of operational resource requirements that have been identified for some initial protocols. We will also include some comparison to what is happening elsewhere across the world in both of these areas, and the next steps in further improving and validating our approach.
66.  **BIRTH ORDER AND SIBSHIP SIZE AFFECT RISK OF LYMPHOID CANCER IN FAMILIES**

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**Category: Translational/Clinical**

**Introduction:** Lymphoid cancers are a heterogeneous group of neoplasms that arise from immune cells. Established risk factors include older age, sex (male), ethnicity, compromised immune function and a family history of hematological malignancies. Early life environment may affect the risk of immune-related disorders, such as allergies, autoimmune conditions, and some lymphoid cancers. The hygiene hypothesis proposes that relative lack of infectious exposures during childhood prevents the optimal maturation of the immune system and subsequent development of adult-onset diseases. Family structure and crowding relate to the hygiene hypothesis as they are likely to affect extent of exposure to infectious diseases, with low birth order and smaller families correlating with high risk of immune-related disorders.

**Methods:** The relationships between lifestyle factors and risk of lymphoid cancer was evaluated using a logistic regression with generalized estimating equation among 196 families with a history of hematological malignancies. We report on data from 441 lymphoid cancer cases and 987 unaffected siblings among 339 sibships. Odds ratios (ORs) and 95% Confidence Intervals (CIs) were adjusted for age, sex, and family structure.

**Results:** Birth order and sibship size were independently associated with risk of lymphoid cancer. Higher birth order was inversely associated with risk of cancer for all lymphoid cancers collectively (OR=0.80; 95% CI:0.74-0.85), and separately for multiple myeloma, non-Hodgkin lymphoma and chronic lymphocytic leukemia, but not Hodgkin lymphoma. That is, individuals with an earlier birth order position had a higher risk of lymphoid cancer than later born siblings. Sibship size was also inversely associated with risk of collective lymphoid cancers (OR=0.82; 95% CI:0.80-0.85), and all subtypes. In addition, high maternal and paternal education, above average income during childhood, allergies (OR=2.36; 95%CI:1.52-3.65) and a tonsillectomy (OR=1.87; 95% CI:1.24-2.84) were independent risk factors for lymphoma.

**Discussion & Conclusions:** The associations between lymphoma and atypical immune function have been explored in small cohort and large population studies, however, there was limited evidence in the familial context. The inverse relationship observed here between family structure and risk of lymphoma is supportive of the hygiene hypothesis, and that childhood infectious exposure may play a role in the risk of multiple types of lymphoid cancers. The association between allergies and lymphoma favour the antigenic stimulation hypothesis wherein chronic stimulation of the immune system eventually leads to random oncogenic mutations and subsequent cancer development. A tonsillectomy in children may indicate recurrent tonsillitis caused by an impaired immune response. Our results provide evidence of an elevated risk of lymphoma among individuals with a high childhood socioeconomic status as a consequence of delayed infection, clean household environment and reduced household crowding. This is the largest study in a familial context that supports the hygiene hypothesis contributing to lymphoid cancer risk and could identify protective lifestyle factors.
67. ADVANCED METHODS FOR CANCER DETECTION BY VAGINAL SCREENING (ADVISE): FEASIBILITY AND ASSESSMENT OF DEEP SEQUENCING BASED SELF-SAMPLING METHODS

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Category: Translational/Clinical

Background: Detection of non-invasive precursors or occult lesions may allow for interventions or cure before progression to advanced, invasive cancer has occurred. Ovarian and endometrial cancer (OC and EC, respectively) are associated with familial cancer syndromes, BRCA-related and Lynch Syndrome respectively. Neither OC nor EC have effective screening tools to help high-risk women detect early lesions or help in decision making around fertility preservation and invasive prophylactic surgeries. Recent studies suggest DNA from vaginal samples may contain tumour-specific somatic mutations and may be useful for monitoring occult/early cancers.

Methods: Cancer affected and healthy women were recruited for minimally-invasive self screening using a vaginal swab and tampon. DNA from swabs, tampons (and tumours in cancer-affected women) were subjected to duplex sequencing targeting 10 genes frequently altered in OC/EC: KRAS, PTEN, ARID1A, PIK3CA, TP53, CTNNB1, POLE, FGFR2, PPP2R1A, and PIK3R1. Samples prepared from vaginal swabs and tampon samples were sequenced to a mean sequencing depth of 3000 and 1800 respectively, allowing reliable detection of variant alleles fraction at 0.2%, and lower in some cases.

Results: To date 17 EC, 3 OV and 9 healthy control specimens have been analyzed. At least one somatic mutation was detected in 16 EC cases and 1 OV case. Common mutations include PTEN (10/17, 59%), ARID1A (9/17, 53%), and PIK3CA (9/17, 53%). Using vaginal swabs, at least one tumour-specific mutation was detected in 9 EC (9/17, 56%) and 1/1 OV cases, while were able detect tumour somatic mutations using tampon samples in all cases (16 EC, 1 OV). Amongst healthy controls, after excluding one sample with significant DNA damage, non-germline mutations were only detected in one sample (TP53, tampon sample). Five cases (4 EC, 1 OV) contained somatic mutations detected in tampon samples which were not detected in the tumour.

Conclusion: The ability to detect tumour-specific mutations using tampon samples for every patient analyzed, coupled with the low number of non-tumour mutations called, indicates that tampons may hold utility in screening for OV and EC. Somatic alterations in normal/non-malignant tissues have recently been reported by others; their significance to potential malignancy is unknown. While our findings of non tumour-specific somatic mutations may represent tumoural heterogeneity, findings of somatic mutations in healthy controls warrants caution as non-clinically significant somatic alterations may confound the development of ultra-sensitive sequencing-based screening strategies.
Transcriptomic analysis is important for understanding the regulatory behaviour of genes. The relative levels of mRNA transcripts within a sequenced sample can reveal deregulated pathways and therapeutic targets in cancers. RNA-Seq allows for unbiased quantification of transcripts. However, large-scale data analysis of RNA-Seq data poses numerous challenges. Specifically, technical artefacts and data pre-processing methods can add excessive noise to the data, confounding pan-cohort analysis and interpretation tasks. Researchers have attempted to overcome these effects by normalizing against a set of housekeeping genes, or by using de-noising methods that simulate and subtract additive noise sources. Recent work in processing single cell data has found that variational inference based approaches can better model the 'true' expression values, and effectively overcome technical noise while providing biological insights.

Our method leverages Bayesian inference within the space of bulk tissue RNA-Seq, approximating the generative distribution from which individual RNA-Seq samples originate. We use this method to re-generate representations of transcriptomes from patients with untreated, primary cancers and adjacent normal tissue. We find that the regenerated representations of housekeeping and ribosomal genes learnt accurately, whereas genes encoding for small RNA species, olfactory receptors, and keratin proteins, are reproduced with less fidelity. The proposed approach also generates a compressed representation of the transcriptome-wide RNA-Seq input, which we show preserves biological relationships within the data. The immediate application of this method lies in identifying genes under strong transcriptional control in a cohort, and for dimensionality reduction.

Keywords:
Medical informatics
Translational medicine
Deep learning
Data and model integration
Model parametrization
Multi-scale models
Transcriptomics
RNA and disease
Machine learning
BC Cancer's Hereditary Cancer Program (HCP) has provided publicly-funded cancer genetic counseling and genetic testing to patients and families at risk of hereditary cancer in British Columbia (BC) and the Yukon since 1996. The emerging use of genetic testing to guide cancer therapies, combined with greater public and healthcare provider awareness, has led to increased demand for cancer genetic services. Consequently, this has resulted in longer wait times for non-urgent new patients at HCP with median wait times of 18 months. The HCP has recently been piloting new service delivery models to optimize efficiency and decrease wait times. In March 2018, we initiated a pilot using a large scale group genetic counselling approach (LSGGC). As compared to the traditional model of one-on-one pre-test and post-test genetic counselling, the LSGGC model involves: 1) pre-test group genetic counselling with a genetic counsellor; 2) post-test one-on-one genetic counselling with a genetic counsellor. Patients eligible for this new approach include unaffected individuals with a family history meeting clinical testing criteria but with no living testable relative available in BC. Families where genetic testing has already been performed in affected relatives, families with a known mutation, cases triaged to be seen by a HCP physician, individuals younger than 19 years of age, and those of Ashkenazi Jewish descent are excluded. Patients are invited to complete surveys including the Genetic Counselling Outcome Scale (GCOS)-24 questionnaire, a Satisfaction survey and the Multidimensional Impact of Cancer Risk Assessment (MICRA). The LSGGC model is being implemented in parallel with traditional one-on-one sessions for comparison. Patients are provided the option of either the LSGGC arm or the traditional arm with the aim to enrol 500 patients between March 2018 and March 2019. To date, five LSGGC sessions have been held (2-42 patients per session) with 92 patients participating in the group sessions, and 91 patients in the one-on-one sessions to date. Both the LSGGC and the traditional arms have shown high patient satisfaction (mean satisfaction scores 3.52/4.00 and 3.71/4.00 respectively). Emerging data presented here shows that a LSGGC model is both feasible to implement and acceptable to patients.
Background: Intratumoral heterogeneity (ITH) is defined as regional differences in phenotypic expression within the same tumor. This heterogeneity may contribute to the inaccurate reproducibility of immunostaining assays and has important implications for accurate tumor classification, epidemiological research and clinical decision-making. Canadian Ovarian Experimental Unified Resource (COEUR) has introduced a small cohort that will serve as a model for tumor heterogeneity in High Grade Serous Carcinoma with the aim to establish benchmarks for ITH in situ, across anatomical sites and over time. We report here on ITH within a primary ovarian site.

Methods: 399 FFPE tissue specimens from 95 patients were used to construct three sets of Tissue Microarray (TMA) for biomarker analysis. A first set (n=21 cases) containing only primary tumors, a second set with primary and secondary tumor sites, a third one with primary and recurrent tumors. Continuous and categorical biomarkers known to be more (e.g. p53) or less (e.g. CD8) homogeneously expressed in HGSC were tested. TMA were stained and scored by an expert pathologist. Two-way random effect intraclass correlation was used to assess continuous markers (CD8) and Fleiss’s kappa was used to test heterogeneity within categorical marker (p53).

Results: As expected, on the first set of TMA, p53 was consistently homogenous within the ovary with (Fleiss Kappa of 1 95%CI; 0.998-1). CD8 was more heterogeneous but showed good reliability within the ovary (ICC 0.769; 95% CI 0.665-0.851).

Conclusion: ITH results for p53 and CD8 within a primary ovarian site are as expected and additional prognostic and diagnostic markers will be added. Next steps will involve comparing heterogeneity across anatomical sites and over time. This work will inform clinical utility of biomarkers.

This project is funded by Terry Fox Research Institute Grant #2009-15.
71. GENE EXPRESSION AND TUMOUR MICROENVIRONMENT IN GLIOBLASTOMA

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Category: Biology/Informatics

Glioblastoma Multiforme (GBM) is a highly aggressive brain cancer with poor prognosis. Despite treatment with surgery, radiation therapy, and chemotherapy, the average survival time is less than two years. Gene expression and copy number analysis by The Cancer Genome Atlas defined four molecular sub-types of GBM and suggested that they could be related to neuronal cell type. They also identified genes and pathways commonly altered in GBM, such as growth factor receptors and tyrosine kinase signaling pathways. The advent of an in vitro model system using brain tumour initiating cells (BTIC) and an in vivo model using orthotopic xenografts in immune-compromised mice allows for testing targeted therapies. However, a thorough understanding of the genome and transcriptome of these models is crucial for the discovery of drugs that will effectively target GBM tumours.

We have performed large-scale genome and transcriptome sequencing of matched pairs of tumour and BTIC samples, as well as matched trios of tumour-BTIC-xenograft. While somatic mutations, copy number variations, and mutation burden are fairly consistent across tumour-BTIC-xenograft samples, gene expression is much more variable. Identifying genes and pathways that differ between tumours and model systems will be important for the use of models in screens for improved GBM therapeutics. Using deconvolution and enrichment methods we find differences in microenvironment composition across GBM subtypes that have prognostic and therapeutic implications. A better understanding of the immune landscape in GBM may provide opportunities for new therapies in this disease that is in dire need of treatment progress.
IDENTIFICATION OF A NOVEL SMALL MOLECULE THAT EXPLOITS A VULNERABILITY TO REACTIVE OXYGEN SPECIES IN LUNG CANCER

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Category: Biology/Informatics

Lung cancer (LC) is the leading cause of cancer-related deaths worldwide, mainly due to the lack of effective drugs available. Through a screen of 189,290 small molecules, the compound LC Screen 3 (LCS3) was identified that inhibits the growth of LC cells but not normal cells. LCS3 is structurally different from most known drugs and its mechanism of action is unknown. Twenty-six LC cell lines were screened and all but two were found to be sensitive to LCS3 (IC50<5µM). Transcriptome and proteome profiling by microarray and SILAC, respectively, suggest that LCS3 strongly induces reduction-oxidation (redox) imbalance. The top 4 predicted upstream transcription factors of LCS3-induced RNA expression changes are all key regulators in the response to oxidative stress (NRF2, MAFK, CEBPB and BACH1). In agreement, flow cytometry with oxidative stress sensor H2DCFDA detected reactive oxygen species (ROS) induction by LCS3 in sensitive cell lines but not in LCS3-resistant cell lines. Notably, the most resistant LC cell line NCI-H1648 has biallelic functional loss of KEAP1, which negatively regulates NRF2-mediated cytoprotective gene expression. We confirmed NCI-H1648 has high basal expression of genes that support redox balance that are likely to confer the observed resistance to LCS3. The antioxidants N-acetylcysteine, GSH-MEE and Trolox partially rescued LCS3-induced cytotoxicity, which further implicates redox imbalance in the mechanism of LCS3-induced cell death. To elucidate the molecular targets of LCS3, we applied thermal proteome profiling (TPP), which identifies thermally-stabilized protein binders with proteome-wide coverage and identified 49 proteins that are putative binders of LCS3. Of the 49 TPP hits, 9 are enzymes involved in redox reactions including glutathione peroxidase 4 (GPX4), glutathione-disulfide reductase (GSR), thioredoxin reductase 1 (TXNRD1), peroxiredoxin 4 (PRDX4) and glutathione S-transferase omega 1 (GSTO1). We will further evaluate these TPP hits through siRNA knockdown and in vitro activity assays to further distinguish LCS3 binders from effectors. Through this work, we aim to use LCS3 as a tool compound to identify a novel cancer dependency that can be exploited for the benefit of LC patients with advanced tumors, for whom treatment is urgently needed.
73. HARMONIZATION OF CELL LYSIS PROTOCOLS FOR GLOBAL PROTEOME PROFILING OF TUMORS

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Category: Biology/Informatics

One of the primary workflows in the GSC proteomics platform is single-pot solid-phase-enhanced sample preparation for clinical tissue proteomics (SP3-CTP), a quantitative global proteome profiling method. This workflow has been shown to provide reproducible protein preparation from a variety of sample types including formalin fixed paraffin embedded tissues, fresh frozen tissues, cell lines, immunoprecipitates, and FACS-sorted cells. A large proportion of the work performed using this method is collaborative and as such we often receive samples prepared by a variety of different protocols containing any number of reagents. For example, a 4 M guanidine buffer might be used with or without mechanical disruption for cell lysis. Additionally, there are different standard lysis buffers for different researchers or projects. To highlight this point, either a detergent concoction that provides good response for the transcription factor FOXL2 by western blot or RIPA buffer might be used by different scientists to prepare samples for proteomics analysis. This heterogeneity in cell lysis protocols is a benefit to targeted work but is a cause for concern for global analysis because each protocol may not provide equivalent extraction of the proteome. As an example, it could be that the buffer developed for FOXL2 extraction is better for extraction of nuclear proteins while a guanidine lysis buffer with bead-beating, a protocol for FFPE tissue extraction, and a general cell lysis protocol resulted in the detection of 4,607, 4,983, and 4,621 proteins and 24,202, 22,790, and 20,279 peptides, respectively. These three protocols also resulted in the highest average protein coverage: 5.3, 4.6, 4.4 peptides were detected per protein respectively. It was also found that for a gentle lysis conditions with the guanidine lysis buffer, the use of mechanical disruption is required for better coverage. For detergent-based lysis buffers, no mechanical disruption is necessary to obtain a satisfactory number of protein detections. Of the three mechanical disruption methods tested, the most efficient was bead beating, as expected. These data will be analyzed to investigate preferential protein extraction based on cell compartment between the different methods. This information will be used to further differentiate the performance of the three best lysis protocols for different experimental objectives and will also be incorporated into targeted protocol development.
Development of a Liposomal Formulation of Copper Diethylidithiocarbamate with Improved Anti-cancer Activity

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Category: Translational/Clinical

Objective: Disulfiram is an FDA-approved drug for the treatment of alcoholism, and functions by producing an acute sensitivity to ethanol. Since the 1970’s, it has also been shown to have an anti-cancer effect in pre-clinical models, as well as in small clinical trials. After oral administration, disulfiram is reduced to diethyldithiocarbamate (DDC), which subsequently requires copper for activity. This complex has low solubility, and previous efforts in our lab to adapt it for therapeutic use have involved liposomal encapsulation. However, the developed formulation forms a precipitate which hinders filter sterilization, and has shown limited efficacy in mouse tumour models. The objective of this project is to develop a formulation that can be filter sterilized and examined further for pharmacokinetics and anti-tumour efficacy in animal models.

Methods: While the previous formulation used copper that was pre-encapsulated in the liposome, a new formulation is described in which DDC and copper are added step-wise into a copper-free liposome made using 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol (Chol). Cu(DDC)₂ loading and cytotoxicity was assessed in ovarian cancer cells, as well as Cu(DDC)₂ loss due to filter sterilization. Fractionation was also performed to determine association characteristics of Cu(DDC)₂ and the liposome.

Results: While both formulations showed similar drug loading and cytotoxicity, the newly developed formulation retained five-fold more of the drug after filtration. Fractionation also showed greater association between liposome and the drug, with a closer co-elution pattern.

Conclusion: We have developed a formulation that shows a greater association of liposome and Cu(DDC)₂, and which can be filter sterilized. Additional pharmacokinetic studies will examine plasma elimination, as the previous formulation experienced rapid release from the liposome upon administration. Anti-tumour efficacy studies will also further examine the therapeutic potential of this formulation.
75. HOW BC CANCER CLINICIANS USE LOCAL DATA TO MAKE EVIDENCE-BASED DECISIONS THAT HELP SHAPE LOCAL POLICY AND PRACTICE

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Breast Cancer Outcomes Unit (BCOU): Co-Chaired By Dr. C. Lohrisch and Dr. A. Nichol

Category: Biology/Informatics

Objective: The BCOU was established in 1994 to facilitate the use of BC Cancer data to (1) inform BC Cancer policy development through evidence-based research, (2) monitor the outcome data collection process to ensure compliance, relevancy, and accuracy of outcomes reporting, (3) facilitate the investigation of clinical questions using local data to inform best practices and for quality assurance, and (4) facilitate the academic development of BC Cancer clinicians, scientists, residents, fellows, and students.

Materials and Methods: The BCOU falls under the auspices of the Breast Tumour Group. A Methods and Priorities group, comprised of breast cancer specialists from a wide range of disciplines, evaluates project proposals on the basis of value, feasibility, impact, and priority. The BCOU is staffed by a Research Coordinator and a Data Analyst, along with the purchased services of a Health Record Administrator I and a Biostatistician. The BCOU database consists of audited demographic, staging, pathology, treatment, and outcome data for over 68,000 breast cancer patients diagnosed since 1989 and referred to BC Cancer. The data is population-based and prospectively collected. Once BCOU and ethics approval have been obtained, the cohort is assembled, data audited for quality, and analyses performed. Study results are written and submitted for publication and/or conference presentation.

Results: BCOU studies have directly influenced BC Cancer treatment policy and supported BC Cancer administration by providing information that informs decisions on the need for various interventions for breast cancer patients. In addition to over 240 published abstracts, the BCOU has had 207 peer-reviewed publications to date, of which 33 involved translational and molecular marker research in collaboration with the Genetic Pathology Evaluation Centre. Three recent examples (referenced below) demonstrate how BCOU studies have influenced clinical practice: 1. Dr. Leong’s study established that using short-course radiotherapy to treat the lymph nodes in the axilla is safe. 2. Dr. Nichol’s study confirmed that, in BC, omitting radiotherapy does not affect the overall survival of women aged over 70 years on hormone therapy. 3. Dr. Wilson’s study identified a population of patients with sufficient recurrence risk after 5 years of adjuvant hormone therapy to warrant continuing therapy for 10 years.

Conclusions: The BCOU is a rich resource for addressing research questions on population outcomes and improving the clinical care of patients with breast cancer in BC.

References:
CDK12 is a transcriptional CDK (cyclin-dependent kinase) that partners with Cyclin K to enhance transcription elongation through the phosphorylation of RNA Polymerase II. It has been classified as a tumour suppressor gene due to recurrent CDK12 alterations found in ovarian and breast cancers and a reported role in the regulation of DNA repair genes. More recently, CDK12 mutations defined a new molecular subtype of metastatic prostate cancer highlighted by focal tandem duplications, increased gene fusions, and elevated neoantigen burden. The molecular mechanisms underlying CDK12 function in normal cells, as well as those driving its mis-regulation in different cancer types, remain unclear. Tumour mutations in CDK12 frequently map to one of its four functional domains: an RS (arginine/serine-rich) domain, a kinase domain, and two proline-rich motifs. While it has been shown that the kinase activity of CDK12 is required to phosphorylate RNA Polymerase II, the presence of other domains suggest additional functions of CDK12 that have yet to be defined. Using mRNA sequencing, we demonstrated that CDK12 regulates a specific subtype of alternative splicing, alternative last exons (ALEs). This regulation was both gene- and cell line-specific, suggesting that CDK12 may differentially associate with regulatory splicing factors or respond to upstream signaling pathways. To test this hypothesis, we performed affinity purification-mass spectrometry (AP-MS) of CDK12 in multiple cancer cell lines and with different epitope tags. In all cell lines examined, we identified a core CDK12 complex that includes Cyclin K, essential components of constitutive splicing (e.g., the Prp19 complex), and RNA processing factors (e.g., the WTAP complex). Notably, interactions between CDK12 and regulators of alternative splicing (e.g., SRSF proteins) differed depending on the cell line. By performing domain deletion analyses, we found that both the RS and kinase domains of CDK12 were required for its interaction with the Prp19 complex, whereas only the RS domain was necessary for its interaction with alternative splicing and RNA processing factors. The combination of common and differential interaction partners suggest a mechanism for how CDK12 can direct a specific subtype of alternative splicing, but in a gene- and cell line-specific manner. Together, these results provide a mechanistic model for alternative splicing regulation by CDK12.
Neomorphic mutations in isocitrate dehydrogenase 1/2 (e.g. IDH1 R123H) and heterozygous inactivating mutations in Ten Eleven Translocation 2 (TET2) methylcytosine (5mC) dioxygenases are mutually exclusive events in de novo acute myeloid leukemia (AML) and account for more than 40% of AML cases. IDH1/2 mutations drive epigenomic dysfunction by producing the oncometabolite R-2-hydroxyglutarate (R-2HG), which inhibits TET2, and is associated with alterations in the methylation levels of CpGs genome-wide. Previously, we established that vitamin C (vitC) induces epigenetic reprogramming through TET activation in an engineered murine leukemic model overexpressing HOXA9 and harbouring a neomorphic mutation in IDH1 (R132H). To further understand the role of TET2 in this reprogramming we performed meDIP-seq and hmeDIP-seq in a murine AML model expressing IDH1 R132H in which Tet2 had been genetically inactivated by CRISPR/Cas9 (TET2KO). TET2KO induced a selective advantage in our cell line over multiple passages and induced methylation changes at enhancers within 20kb of genes associated with inflammatory signaling. Examination by immunohistochemistry of the TET2KO line following exposure to 0.3mM vitC treatment for 12 hours showed a reduction in total 5hmC gain compared to the parental line. Analysis of the hmeDIP-seq datasets generated following vitC treatment showed induced local gains in 5hmC in both R132H and TET2KO specifically at regulatory regions previously annotated to be marked with H3K27ac and H3K4me1 marks in R132H, though to a lesser extent in the TET2KO line. Regardless of TET2 status, vitC induced a directional gain in 5hmC at regions shown to be hypermethylated by mutant IDH1. These common regions were associated with genes implicated in apoptosis and hemopoiesis and were enriched in PU.1 binding sites, while regions uniquely hydroxymethylated in R132H were associated with genes implicated in DNA repair mechanisms. Taken together, this suggests a model in which TET3, which is expressed at similar levels in AML, may perform some redundant functions similar to TET2 after vitC induction.
BAF COMPLEX MUTATIONS DYSREGULATE ENHANCER LANDSCAPES IN MALIGNANT Rhabdoid Tumor and Ovarian Clear Cell Carcinoma

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TFRI Project Title: The Terry Fox New Frontiers Program Project Grant in New Vistas on Cancer Biology and Treatment: Conceptual Advancements from the Forme Fruste Project
Project Leader: David George Huntsman

Category: Translational/Clinical

Background: Genetic mutations to members of the mSWI/SNF(BAF) complex are recurrent events in cancer and are thought to contribute to carcinogenesis. Cancer subtypes show remarkable specificity to BAF subunit loss (e.g. SMARCB1 in malignant rhabdoid tumor (MRT); ARID1A in ovarian clear cell carcinoma (OCCC)). BAF complexes play important roles in transcriptional regulation but the drivers of selection for specific subunit disruption in cancer subtypes is currently unknown.

Methods: To investigate the role of SMARCB1 and ARID1A in MRT and OCCC, we performed ATAC-seq, native ChIP-seq (H3K4me3, H3K4me1, H3K27ac, H3K27me3, H3K36me3, H3K9me3) for histone modification and RNA-seq on MRT and OCCC isogenic cell line models: the MRT cell line G401 engineered to re-express SMARCB1 (G401-B1), and an OCCC line engineered with a biallelic loss of ARID1A (AC14).

Results: In our MRT model we identified 3269 and 2398 open chromatin regions in the presence and absence of SMARCB1 respectively, of which 1624 (49.7%) were found only in the presence of SMARCB1. Moreover, we identified an increase in the number of active enhancers, as defined by the presence of the H3K27ac and H3K4me1, in the presence of SMARCB1. FOXO1 is the most significantly enriched binding elements in the SMARCB1 specific enhancers and gene enrichment analysis of transcripts up-regulated in G401-B1 cells compared with G401 showed enrichment in genes implicated in cell morphogenesis and differentiation.

In contrast loss of ARID1A did not result in a global change of chromatin accessibility with equivalent gains and losses of open chromatin regions observed in the presence and absence of ARID1A. Instead, ARID1A loss altered chromatin accessibility in a context specific manner, largely at active enhancers (H3K27ac marked) but not primed enhancers (H3K4me1 marked). ARID1A loss was also associated with a decrease in the number of super-enhancers and motif analysis of ARID1A dependent super-enhancers revealed enrichments for ATF3, AP-1, BATF and Jun-AP1 motifs, as well as tissue specific transcription factors such as RUNX, MafK and Bach2.

Conclusion: Our analysis revealed that SMARCB1 and ARID1A loss is associated with subunit specific genome-wide chromatin dysfunction leading to distinct enhancer alterations and differential gene expression.
Background and Methods: Lung cancer remains one of the deadliest forms of cancer worldwide as clinical symptoms typically present only in the late stages of disease. Despite improved detection and survival arising from the advent of low-dose computed tomography (LDCT), this screening modality suffers from a high false-positive rate, often leading to invasive procedures which may result in unnecessary complications. In this study, ultra-high resolution CT images were obtained to assess the feasibility of differential diagnosis of non-small cell lung cancer (NSCLC) through qualitative characterization and radiomic analysis of tomographic images. The ability to confidently classify malignancy from benignity in a lung nodule using this proposed non-invasive tool could substantially reduce the number of biopsies that are currently used in the process of diagnosis.

Results: A qualitative characterization of the critical differentiating histological features of squamous cell carcinoma (SCCa) and adenocarcinoma (ACa) were visible in the tomographic images, using the histopathological images as reference. 169 radiomic features were also extracted from approximately 30,000 images. Of these features, 6 were identified that showed promise in a positive identification of a malignant nodule.

Conclusions and Impact: Our results demonstrate that the tomographic characterization of the discriminating features of histological subtypes of NSCLC is possible at ultra-high resolution. Our preliminary results also demonstrate that the radiomic characterization of selective features can differentiate cancerous from benign nodules. This potential reduction in the need for biopsy offers many patient benefits, including reduced risk of surgical complications and reduced patient anxiety, while increasing overall quality of life. Future work needs to be continued to determine if these radiomic features can detect discriminating features of histological subtypes of NSCLC in vivo and to determine the minimum resolution required to detect these features.

This research was partially funded by the BC Cancer Foundation and by Service Canada.
INTEGRATION OF A WEB-BASED FOLLOW-UP PLATFORM INTO BC CANCER FOR IMPROVING QUALITY OF LIFE CARE AND RESEARCH

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Category: Biology/Informatics

Background and Methods: This project evaluated the feasibility of implementing an online system to collect long-term patient-reported outcomes (PROs) and to contact patients after being treated for cancer at our centre. Eight hundred patients were surveyed between April 2016 and March 2018. Eligible participants include English speaking individuals 18 years or older who have attended at least one appointment at our centre. To evaluate contact and follow-up preferences, surveys collected information on internet access, preferred methods for follow-up or contact and likelihood of using an online follow-up system. Follow-up method choices include online, mail and phone. Choices for contact include email, mail, phone and text message. Survey data was supplemented with demographic information from participant's charts.

Results: Males and females participated equally (51% male, 49% female). Most participants (54%) live within 50 km of driving distance from our centre, while 31% live between 51-200 km away, 9% 201-400 km away and 6% a distance greater than 400 km or responded “N/A”. Of survey participants, the most common diagnosis was breast cancer (23%).

The majority of participants preferred an online method as primary contact method (59%). Mail (18%), phone (16%) and text (<2%) were otherwise preferred. Remaining participants expressed no preference or “wish for no contact” (6%).

An online system was the preferred method for PRO collection, a means of follow-up which would take place in addition to routine in-person appointments. Participants preferred an online system (61%) over other options of phone (20%) or mail (17%). Only remaining participants (2%) did not wish for any follow-up with the clinical team at our centre.

Conclusions and Impact: Based on our analysis, web-based communications will be well-received and a feasible method for long-term follow-up with patients treated at our centre. Further research will evaluate how use of a successful online follow-up system will improve communication and evaluation of patient outcomes after treatment during the survivorship period.

This work was supported by the UBC Faculty of Medicine, Summer Studentship Research Program.
82. DETERMINING THE FUNCTIONAL ROLE OF TRAF3 DELETIONS IN DIFFUSE LARGE B CELL LYMPHOMA

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Category: Biology/Informatics

Background/objectives: Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (30-40%) and is fatal without rapid treatment following diagnosis. Despite recent breakthroughs in the characterization of the disease using genomics and transcriptomics approaches, approximately a third of people with DLBCL receiving the standard therapeutic regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) experience relapse and are not cured. The biological heterogeneity of clinical responses remains to be fully elucidated. A recent study by our lab analyzing genomic variations and gene expression profiles of 139 diagnostic DLBCL samples from human subjects treated uniformly with R-CHOP revealed that recurrent deletion of the tumour necrosis factor receptor-associated factor 3 (TRAF3) gene was correlated with poor 5 year progression free survival. In B cells, TRAF3 negatively regulates the canonical and non-canonical NF-κB pathways and plays a central role in survival and germinal center formation. Importantly, TRAF3 inactivation results in constitutive NF-κB activation, a hallmark of the activated B cell (ABC) cell-of-origin subtype of DLBCL. Our objective is to further investigate the molecular mechanisms of TRAF3 biology which potentially contribute to DLBCL pathogenesis.

Methods: We generated TRAF3-deleted human ABC- and germinal center B cell (GCB)-DLBCL cell lines using CRISPR/Cas9 genome editing technology in order to model and to assess NF-κB pathway activation and cell proliferation. Guide RNA sequences were designed to target the first translated exon of TRAF3 to induce premature protein truncation. TRAF3 status in isogenic cell line clones was validated using a combination of Sanger sequencing and western blotting. NF-κB activation was determined by western blotting of canonical and non-canonical pathway components, and cell proliferation was measured using the WST1 assay.

Results: Screening of CRISPR/Cas9 genome edited single cell isolated revealed mono-allelic and bi-allelic frameshift deletions of TRAF3 in both ABC- and GCB-DLBCL cell lines. In the GCB-DLBCL cell line DOHH2, we found that loss of TRAF3 confers an increasing trend of proliferation under non-stimulated conditions. Moreover, phosphorylated-AKT protein expression and CD69 surface expression are upregulated in TRAF3 mutants, suggesting that these cells may have survival advantages and anti-apoptotic properties.

Conclusions: Our results raise the possibility of TRAF3 as a novel tumour suppressor in GCB-DLBCL. Ongoing work will aim to investigate NF-κB activation and R-CHOP sensitivity in TRAF3-deleted ABC-DLBCL cell lines and to elucidate drug targets for therapeutic intervention.

The authors declare no conflicts of interest.
Background: Endometrial cancer is the 4th most common cancer in North American women. Among gynecological malignancies, endometrial cancers are the most common and 2nd most lethal. In contrast to several other major cancers, for which the death rates have decreased in recent years, the mortality rate for endometrial cancer continues to rise, likely due to increased incidence of advance-stage tumors and high-risk histologies. These high-risk tumors are generally high grade and display aggressive and metastatic behaviour. Although they account for ~25% of cases, they are responsible for ~75% of deaths from endometrial cancer.

Betacellulin is a member of the epidermal growth factor (EGF) family. Overexpression of betacellulin has been demonstrated in several human cancers and is associated with tumor growth and invasion, reduced survival, and resistance to targeted therapies. Normal endometrium has been shown to express betacellulin and EGF family receptors, and studies suggest betacellulin is overexpressed in endometrial cancer. However, the functions and clinical relevance of betacellulin in endometrial cancer are unknown. In this study, we tested the hypothesis that betacellulin enhances the viability, migration, and/or invasion of endometrial cancer cells.

Methods: The cBioPortal for Cancer Genomics was used to query 178 cases of grade 3 endometrial carcinoma from The Cancer Genome Atlas (TCGA; 112 endometrioid, 53 serous, and 13 mixed histology) for down-regulation of betacellulin mRNA (lower quartile). KLE, HEC50, HEC1A and HEC1B endometrial cancer cell lines were serum starved for 24 hours prior to treatment with or without recombinant betacellulin (50 ng/mL). Protein and mRNA levels were measured by Western blot and RT-qPCR. MTT assay was used to measure cell viability 24, 48 and 72 hours after treatment. Effects of betacellulin on cell migration were examined by treating cells for 24 hours prior to assessing 24-hour transwell migration with uncoated inserts. Cell invasiveness was measured for 48 hours in Matrigel-coated transwell inserts following treatment with betacellulin for 24 hours.

Results: Kaplan-Meier analysis showed that tumors with betacellulin mRNA levels in the lower quartile had much better overall and disease free survival (Log-rank test \( P = 0.00635 \) and 0.00991, respectively). BTC mRNA was detected in all four cell lines however KLE and HEC50 cells had higher intrinsic expression levels. Whereas all four cell lines had comparable mRNA levels of HER1 and HER2 EGF family receptors, HER4 mRNA and protein levels were considerably higher in KLE cells. Treatment with betacellulin significantly increased the viability of all four cell lines at 72 hours. In addition, betacellulin treatment significantly enhanced the migration and invasion of all four cell lines.

Conclusions: Our results suggest that betacellulin may contribute to poor survival in high grade endometrial cancer, perhaps because of its ability to promote endometrial cancer cell growth, migration, and invasion.
RESULTS OF A CLINICAL TRIALS SURVEY OF ONCOLOGISTS AT BC CANCER - VICTORIA

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Category: Translational/Clinical

Background: BC Cancer – Victoria (VIC), is one of six regional cancer centres in BC with the second highest volume of cancer patients in the province, providing a rich environment for conducting clinical trials. Since 2006, 1370 accruals into clinical trials conducted at VIC (585 into systemic therapy trials and 785 into radiation trials) have occurred. Following a decline in the activity within the systemic therapy trial portfolio, a new clinical trials manager was hired to bring the two trial groups together under a common Clinical Trials Unit structure and to reinvigorate clinical trial activity. A survey was designed to establish the level of interest in clinical trials among VIC oncologists.

Methods: The survey contained 26 items, 21 of which were Likert-based response items and 5 were free-text. All VIC oncologists were invited to complete the survey between July and September 2018. Survey questions focused on past experience with clinical trials, opinions about possible clinical trial barriers at VIC, preferences for future clinical trials and to solicit suggestions for improving the future conduct of clinical trials at VIC. Survey responses were collated in Excel and summary statistics compiled.

Results: The survey completion rate was high at 92% with 21/22 medical oncologists (MOs) and 14/16 radiation oncologists (ROs) responding. 86% of ROs and 48% of MOs reported having 7+ years of clinical trial experience. 79% of ROs and 62% of MOs had been a Principal Investigator (PI) on one or more clinical trials. 71% of ROs and 67% of MOs were interested in being a PI on a future clinical trial whereas 86% of ROs and 76% of MOs were interested in being a co-investigator on a future clinical trial. The survey identified several perceived barriers to conducting clinical trials: 71% of oncologists agreed that there are not currently sufficient human resources at VIC for more clinical trials; 71% agreed that within the last few years trials could not be initiated due to administrative hurdles; 69% agreed that the documentation effort of clinical trials is too large; 60% agreed that the documentation effort within their daily clinical routine hampered them to recruit patients into clinical trials; and 29% agreed that conflicts within VIC negatively interfere with recruitment activity. 69% of oncologists had no preference over recruiting to industry or academic-sponsored trials (19% of MOs expressed a preference to solely recruit to academic-sponsored trials). ROs expressed a greater awareness, 56% vs 43% of MOs, of the clinical trials available within the CCTG/3CTN portfolios for their disease sites. 37 specific suggestions were put forward from 28 oncologists on how to improve the future of clinical trials at VIC. The majority of the suggestions related to the need for increased resources and support, and improved processes and efficiencies for VIC clinical trials.

Summary: The results of the survey suggest that there is enthusiasm for conducting clinical trials in systemic and radiation oncology at VIC; however, there are administrative and structural burdens that may impede participation unless addressed. The MO team has physicians who are newer to clinical trials and would likely benefit from a clinical trials mentorship program. Work is underway to update local VIC clinical trial processes for all stages of a trial. The strategic plan for the VIC CTU includes careful trial portfolio development and staff growth that is both feasible and sustainable.
85. EPIGENETIC REPROGRAMMING IN A HUMAN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA MODEL

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Presenter is a PhD graduate student.

Research Project: TFRI Leukemia Program Project Grant (PPG)

Category: Biology/Informatics

T-cell acute lymphoblastic leukaemia (T-ALL) is an aggressive blood cancer of malignantly transformed immature thymocytes. While epigenetic reprogramming has been implicated in the initiation of T-ALL the lack of an in vitro model and appropriate normal controls has hampered the quantitative measurements of epigenetic signatures associated with T-ALL. To address this challenge we have performed temporal epigenetic and transcriptome profiling of a novel human T-ALL model and untransformed controls. In this model, cord blood derived CD34+ cells are transduced with a constitutively active NOTCH1 allele, TAL1, BMI1 and LMO2 and cultured in vitro under conditions that promote T-cell differentiation. Three time points following transfection (Day 14, 24 and 47) were collected for epigenetic and transcriptome profiling. Hierarchical clustering of protein coding gene expression and H3K27me3 or H3K4me3 promoter density separated transduced from non-transduced CD34+ cells regardless of the in vitro collection day. In comparison to parental CD34+ cells profiled prior to in vitro culturing, both of the transduced and non-transduced CD34+ cells showed directional increases in the genomic space occupied by H3K4me3. Furthermore, the transformed CD34+ cells showed increased genomic H3K4me3 occupancy compared to non-transduced normal comparators, the directionality of which was observed consistently across all three time points. Surprisingly, unique genomic regions consistently marked by H3K4me3 in the transduced cells were associated with gene bodies and intergenic regions rather than gene promoters as might be expected for this mark. Enrichment analysis of genes containing genomic regions uniquely marked by H3K4me3 in the transduced cells were significantly enriched in terms relevant to leukemic biology. A subset of uniquely H3K4me3-marked regions were co-localized with H3K27ac peaks, enriched in ETS and RUNX binding motifs and showed transcription reads emanated specifically in the transduced cells, implying regulatory roles. Similar directionality was observed in H3K27me3 occupancy in transduced CD34+ cells vs. their non- transduced controls. Regions that lost H3K27me3 in the transduced cells were enriched in TAL1 motifs, consistent with its known role in driving an oncogenic transcriptional program. Integrative analysis of epigenetic and transcriptional alterations associated with T-ALL transformation allowed for the identification of putative targets of the transduced oncogenes. In summary, the dynamic epigenetic reprogramming revealed by this study has led to new insights into the mechanisms of T- ALL initiation and has the potential to provide novel therapeutic targets in the future.
86. OPTIMISING HEALTH CANADA APPROVED IMAGE CYTOMETRY SYSTEM FOR ORAL CANCER SCREENING

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Category: Biology/Informatics

Objectives: Cytology, such as cervical pap smear, has provided an excellent non-invasive screening tool in early cancer detection and management guidance. Previously published results from our group using Feulgen-thionin stained oral brushing samples and in-house imaging system have shown that abnormal samples could be distinguished from normal with 89.3% sensitivity and 96.5% specificity. ClearCyte (Perceptronix Medical Inc.) is a Health Canada approved image cytometry system that can detect gross alterations of nuclear DNA content representing chromosomal aneuploidy, a biomarker of malignancy. The system has been used on oral, lung, cervical and prostate cytological samples. In our recent analysis on oral brushing samples, this commercialized system failed to recognise the majority of the oral cancer brushing samples. This high false negative rate is worrisome. The purpose of the current study is to test whether a newly developed algorithm can improve the specificity and sensitivity in differentiating normal and abnormal oral brushing samples.

Methods: A set of 146 oral brushing samples of high-grade dysplasia (n=42) and cancer (n=104) were retrieved from a pan Canadian surgical trial. The cells of each sample were cytospun onto glass slide, stained with Feulgen-thionin nuclear stain and scanned on ClearCyte. The criteria of ClearCyte of positive call are the presence of ≥ 400 valid nuclei and ≥ 5 nuclei with DNA content ≥ 2.3. A new decision tree was created using a proprietary program, Review (BC Cancer). A subset of 10 samples with low number of total nuclei detected by ClearCyte system was tested with this new algorithm. The means of total and abnormal nuclei counts were compared between ClearCyte and the Review outputs. Preliminary statistical analysis was performed using IBM SPSS Statistics V25. A two-tailed Student t-test was used to compare the mean nuclei counts for ClearCyte and the Review.

Results: According to the criteria of positive call for ClearCyte, 126 out of 146 (86.3%) samples were scored as negative. After reviewing each case, this may be attributed to the design in software which leads to rejection of numerous valid nuclei resulting in low nuclei count. For the 10 samples analyzed, the developed algorithms using Review program were able to detect an average of 7.2 times more total nuclei than ClearCyte software (p=0.01). It also identified an average of 3.6 times more abnormal nuclei (p=0.04). Among 9 samples scored negative using ClearCyte, 8 samples were scored positive using the Review program.

Conclusions: Our preliminary results showed an encouraging improvement to the ClearCyte DNA ploidy analysis with the use of a new decision tree. With the improved detection algorithms, we are able to not only recognise thousands of more individual nuclei rejected by ClearCyte system as junk, but also potentially increase the sensitivity and specificity of image cytology in differentiating abnormal from normal samples. Further refinement of the algorithms and testing them using larger sample size can revive the application of this system.
87. OPTIMIZED MOLECULAR RISK STRATIFICATION FOR OVARIAN ENDOMETRIOID CARCINOMAS


*Presenting author is an undergraduate trainee in the laboratory of Dr. Anglesio.

Category: Translational/Clinical

Background: Endometrioid ovarian carcinoma (ENOC) accounts for greater than 10% of ovarian carcinomas and is typically associated with a favourable prognosis compared to other histotypes. Prognostication is important for patient management. Our group has previously derived a validated and clinically relevant prognostic tool, ProMisE, as a surrogate to classify the four TCGA molecular subtypes of endometrial carcinoma. Our aim was to validate the prognostic associations of ProMisE in ENOC using established immunohistoc hemical (IHC) assays and custom tagged-amplicon sequencing assay for POLE exonuclease-domain hotspot mutations.

Design: 218 ENOC cases from the COEUR cohort were subjected to POLE sequencing. As specimens originated from low quality, archival tissue, we derived a custom, 3-fold redundant design of amplicons over each POLE hotspot. Amplicon performance was monitored by qPCR and sequencing done on Illumina MiSeq. Mutations were considered ground truth if observed in ≥2/3 overlapping amplicons, orthogonal validation is ongoing. POLE data was combined with IHC results to assign cases into four groups as per ProMisE guidelines: (1) mismatch repair deficient if any of the four MMR proteins were absent (MMRd), (2) POLE exonuclease domain mutated (POLE), (3) p53 mutant (p53abn) or (4) p53 wild type (p53wt) based on immunohistochemistry. Kaplan-survival analysis was performed; outcomes and proportions of each class were compared to endometrial cancer counterparts.

Results: The majority of cases were p53wt (77%), followed by MMRd (13%), p53abn (7%) and POLE mutated (3%). Our observed frequency of POLE mutations is consistent with previous reports and orthogonal validation has not detected false positive or false negative hotspot mutations. With respect to ProMisE outcomes, p53abn cases had the highest risk of recurrence (HR=3.5, 95%, CI 1.60-6.99) compared to p53wt. The risk of recurrence was reduced for POLE exonuclease domain mutated cases (HR=0.47), and there was no difference for MMR deficient cases (HR=1.13, CI 0.41-2.50).

Conclusion: Our tagged-amplicon sequencing is a cost-effective and robust assay for detection of POLE hotspot mutations in a research context. ProMisE stratification of ENOC was also highly similar to uterine carcinoma counterparts with only moderate shifts in the proportions of each class. Our data are consistent with a strong etiological and biological link between these cancers.

This project is supported by Terry Fox Research Institute’s Canadian Ovarian Experimental Unified Resource (COEUR).
Advanced and metastatic tumours contribute to the bulk of cancer mortality. However, the majority of efforts to sequence and characterize cancer genomes have been focused on primary, untreated tumours. In the Personalized OncoGenomics program, we have sequenced over 500 adult advanced tumours from a diverse array of cancer types including breast, colorectal, lung, and pancreatic cancers. In addition to providing potential treatment options for these patients, this data also gives insight into the molecular landscape of advanced tumours, the impact of prior therapy in shaping these tumours, and the interaction between the tumour and immune microenvironment.

Whole genome and transcriptome sequencing yielded a total of over 8 million somatic variants, including substitutions, insertions and deletions, copy number changes, and structural variants. Recurrently mutated regions in this advanced cancer cohort varied by cancer type, and included both coding and noncoding events. De novo discovery of mutation signatures identified novel signatures, one of which is associated with prior treatment with the chemotherapeutic agent cisplatin. Germline pathogenic mutations were also associated with specific mutation signatures. Transcriptome profiles were compared to primary tumours, indicating that pathways dysregulated in these previously treated tumours include those related to drug metabolism. The presence of infiltrating immune cells was inferred from transcriptome data; clustering identified a subset of tumours with high levels of T cell infiltration which was independent of tumour type, and this infiltration is associated with better response to subsequent checkpoint inhibitor therapy. These genomic profiles demonstrate the impact of prior therapy and advanced stage on both the genome and transcriptome of tumours.

Genome and transcriptome information identified clinically actionable targets in ~80% of sequenced cases, nearly half of whom received genomically informed therapies. Our results emphasize the importance of whole genome and transcriptome sequencing of advanced cancers in conjunction with clinical data on patient therapies. Integrating this data leads to both biological and therapeutic insights which can guide research and treatment and ultimately have the potential to improve outcomes for these deadly cancers.
Background: Prostate cancer is the second leading cause of male-related cancer deaths in the Western world. Primary treatments are often successful, yet 20% of patients will have recurrence after radical prostatectomy or radiation therapy. Most prostate cancers are dependent on the androgen receptor (AR) for growth and survival. AR is a ligand activated transcription factor that mediates the effects of androgen. The standard care for advanced prostate cancer is androgen deprivation therapy (ADT) or castration. ADT induces disease regression but is not curative. Most disease will progress to the lethal form known as castration-resistant prostate cancer (CRPC). ADT induces oxidative stress in prostate cancer cells, and oxidative stress has been implicated in the conversion of androgen-dependent disease into CRPC. Cellular redox states engage numerous genes and signaling pathways involved in oxidant defense and drug metabolism. Binding profiles of many molecules depend on their redox form. Current drug strategies target the AR C-terminus ligand-binding domain, i.e. Enzalutamide, a second generation anti-androgen. Ralaniten, a novel first-in-class drug, inhibits AR signaling by binding tau-5, in activation function-1, of the N-terminal domain of the AR. We hypothesized that the ability of Ralaniten to inhibit the AR could be affected by cellular redox status. This was investigated by co-administration of the redox inhibitor N-acetylcysteine (NAC) in cultured LNCaP cells.

Results: Preliminary findings from luciferase reporter assays for AR transcriptional activity shows that combination treatment yielded enhanced inhibition of AR transcriptional activity, compared to Ralaniten monotherapy. Combination of NAC with Ralaniten resulted in a statistically significant decrease of the EC50 for Ralaniten.

Conclusions: Inhibition of AR transcriptional activity by Ralaniten was enhanced with NAC. This modulation demonstrates the complexity of cellular mechanisms which influence the efficacy of targeted therapeutics.
90. USING QUANTITATIVE CYTOLOGY TO CONDUCT COMMUNITY ORAL SCREENING AMONG SOUTH ASIANS IN BRITISH COLUMBIA

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Category: Population Health/Health Services

Introduction: Oral cancer is the sixth most common cancer in the world, with more than 300,000 cases diagnosed annually. South Asian countries like India, Pakistan, Sri Lanka and Bangladesh show high prevalence of this disease due to rampant use of chewing tobacco, betel quid and areca nut. This disease has a high mortality rate (~50% 5-year survival) mainly due to the advanced stage at which it is diagnosed. It is purported that majority of oral cancers develop from premalignant lesions, which often present clinically as white or red mucosal patches which can be easily detected by oral health care providers during routine check-ups. New immigrants often face challenges due to limited income, lack of dental insurance, and barriers to accessing dental care which limits their access to receive opportunistic oral cancer screening. Community oral cancer screening and early diagnosis of precancerous lesions can lead to a significant decrease in mortality rates. Quantitative Cytology (QC) uses an automated scanner to quantify DNA content and nuclear morphometric changes in epithelial cells. DNA aneuploidy has shown to be an effective marker of malignant transformation in different studies. The aim of this project was to include quantitative cytology to routine extraoral, intraoral examination and to fluorescence visualisation (FV) to assess its effectiveness in identifying high risk lesions among visually suspicious lesions.

Methods: Demographic information (gender, age, country of birth, ethnicity, risk habit information and dental usage) were collected from the participants who attended the community oral cancer screening day in Surrey, British Columbia. Extraoral, intraoral examination and fluorescence visualisation was conducted, and results were recorded. In patients with no suspected lesions, a brushing was collected from the cheek using a Cytobrush. If a lesion was present and/or there was loss of fluorescence, an additional brushing of that area was collected. The brushings were transported in CellSolutions™ General Cytology Preservative Vial to the lab. Thin-layer cytology slides will be processed from the cell suspensions and then stained using Feulgen Eosin. The slides will be scanned using the MoticEasyScan Infinity at BC Cancer which uses machine learning classification algorithms to identify single, in-focus epithelial nucleus. More than hundred features will be calculated on each of them, such as DNA amount (DNA ploidy), DNA chromatin textures, nuclear shape and size. Cells will be classified as abnormal based on combination of these features.

Results: 305 patients attended the community screening. A total of 20 patients were suspected to have oral potentially malignant lesions. 12 of them were referred to our Next Gen Oral dysplasia clinic for biopsy and 8 were booked for reassessment after 3 weeks. Among all those with high risk lesions, all were tobacco chewers and lacked access to regular dental care. A total of 320 samples were collected which primarily consisted of normal control brushings and additional lesion brushing if suspected. We hypothesize that QC would help to identify abnormal cells and distinguish it from inflammatory lesions which show false FV positivity thus improving the sensitivity and specificity of oral cancer screening.

Conclusion: QC can thus serve as a painless, non-invasive and quick screening tool which can lead to substantial improvement in survival rates especially in developing countries.

Conflict of Interest: None
91. MEDICAL ONCOLOGIST PERSPECTIVES ON THE OUTCOMES OF THE IDEA COLLABORATION

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Category: Population Health/Health Services

Background: Historically, 6 months (mo) of FOLFOX/CAPOX was the standard adjuvant treatment (tx) of stage III colon cancer. In sub-group analyses of the IDEA Collaboration, 3 mo of adjuvant chemotherapy was shown to be non-inferior for patients with T1-3 and N1 tumors, and 3 mo of CAPOX was non-inferior to 6 mo regardless of risk. The real-world uptake of this data and prescribing patterns are unclear.

Methods: A list of questions developed by 4 medical oncologists regarding the views of physicians who treat GI cancers towards the results of the IDEA collaboration were formulated and distributed using an online survey (REDCap). Physicians were recruited using email lists from the Canadian Clinical Trial Group, the Australasian GI Clinical Trials Group, the GI Cancers Alliance (US), the Brazilian Society of Clinical Oncology, and the Thai Society of Medical Oncology. Descriptive statistics and chi-square tests were utilized to summarize information.

Results: Of 165 responses, 138 were complete and included for analysis. Responses originated from South America (55%), Canada (25%), Asia (7%), Australia/Oceania (7%), United States (4%), and Europe (1%); 59% of responders have been in practice for ≥10 years, and practice settings were balanced (academic 34% vs. community 30% vs. both 36%). Most clinicians (98%) were aware of the IDEA Collaboration, and 70% indicate that it changed their practice. Prior to IDEA, FOLFOX was preferred over CAPOX (83 vs. 17%) except in Asia (CAPOX vs. FOLFOX, 60 vs. 40%, p<0.05). Subsequent to IDEA, rates of preference for CAPOX increased (52 vs. 48% for FOLFOX), which was consistent across prescriber location, gender, practice setting, and practice duration (all p>0.05). Most responders (74%) interpret the study as supporting 3 mo of tx for a subset of patients. The preferred approach is 3 mo for T1-3N1 (67%); however 30% of prescribers continue to consider the standard of care still 6 mo, and 3% consider 3 mo to be standard tx for all stage III disease. Those from Australia and Canada are more likely to tailor duration based on disease risk (89% and 78%, p<0.05 vs. other locations). Following IDEA, more oncologists (77%) stated that they are willing to discontinue oxaliplatin early if toxicities develop. Half of responders (49%) found the IDEA trial increased their confidence in decision making for adjuvant tx; 36% were unchanged and 15% indicated decreased confidence.

Conclusions: Prior to the IDEA study, most oncologists preferred FOLFOX but real world survey data shows a shift in preference favoring CAPOX. The majority of clinicians are now prescribing 3 months of adjuvant tx for low risk stage III cancers and are more willing to discontinue oxaliplatin early.
92. MULTISPECTRAL IMAGING FOR DETECTION OF PRECANCEROUS REGIONS IN THE CERVIX USING DEEP LEARNING

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Category: Biology/Informatics

Background: Cervical cancer develops over several years; screening and early diagnosis have decreased its incidence and mortality. Patients thought to have high-grade squamous intraepithelial lesions (HGSIL) underwent imaging with a Multispectral Digital Colposcopy (MDC) prior to the loop excision operation on the cervix.

Study design and methodology: MDC acquires 6 images; reflectance (white, Blue, and violet) and fluorescence excitations (blue, violet, and UV). The pathology status of epithelium within all the sectioned specimen was mapped by the study histopathologist blinded to the MDC data. This map was used to define areas of HGSIL in the excised tissue. Eleven reviewers mapped the histopathologic data back into the MDC images. The reviewers’ maps were superimposed and areas of agreement were calculated. We designed and implemented various Deep Convolutional Neural Networks to discriminate the abnormality areas from the normal tissue using MDC images. We then compared our results with conventional classifiers such as boosted tree and a previously developed ensemble classifiers.

Results: When we applied the classifier to a test set using our hand-engineered features, we obtained an accuracy of 81%, however, using deep neural network we obtained >83% accuracy. Although the accuracy didn’t improved significantly we completely removed the necessity to design hand-crafted features and we hypothesize this will help to generalize our methodology and increase the robustness of our system.

Conclusion: We obtained promising results which shows that using a deep neural network on MDC images could be used as an adjunct to colposcopy and would result in higher diagnostic accuracy compared to existing diagnostic methods.
SOMATIC MUTATION-ASSOCIATED T FOLLICULAR HELPER CELL ELEVATION IN LUNG ADENOCARCINOMA

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Category: Biology/Informatics

Background: T follicular helper cells (Tfh) play crucial roles in the development of humoral immunity. In the B cell-rich germinal center of lymphoid organs, they select for high-affinity B cells and aid in their maturation. While Tfh have known roles in B cell malignancies and have prognostic value in some epithelial cancers, their role in lung tumour initiation and development is unknown.

Methods: 83 pairs of lung adenocarcinoma (LUAD) tumours and adjacent non-malignant tissue were obtained from the BC Cancer Agency (BCCA). Gene expression profiles were generated using the Illumina WG6 microarrays. Relative immune cell fractions were enumerated using CIBERSORT in the BCCA cohort and in two validation cohorts (TCGA, n= 517 LUAD and 59 non-malignant tissue; Stage I LUAD cohort: n= 32 LUAD and 32 non-malignant tissue). The immune cell patterns obtained through deconvolution were confirmed by immunostaining for CD3/CD8/CD79a (panel 1) and CD8/PD1/PDL1 (panel 2) on tumour tissues from 20 of the 83 BCCA patients. A total of 93 regions were independently evaluated in triplicate for immunohistological quantification of tertiary lymphoid organs (TLO) and Tfh cells.

Results: Through immune cell deconvolution, we observed significantly increased Tfh in LUAD than in paired non-malignant tissue in two independent cohorts (mean fold change: 4.33 in the BCCA cohort, p<0.0001; 3.28 in the TCGA cohort, p<0.0001). Tfh density was associated with abundance of plasma cells and high expression of BATF, a transcription factor that regulates B cell class-switch recombination and Tfh differentiation. In a subset of tumours that were stained for T and B cells using multicolour immunohistochemistry, we observed tumour-adjacent tertiary lymphoid organs in 17/20 cases, each with an average of 76 Tfh per section and 16 Tfh observed in the germinal center. Assessing Tfh and plasma cell marker expression through tumour progression by stratifying the TCGA LUAD dataset, we found that the Tfh infiltration is present in every stage of LUAD. This was confirmed in an independent cohort of 32 stage I LUAD. Importantly, Tfh levels were correlated with the number of non-silent mutations/Mb and the expression of MAGEA1 and MAGEA3 antigens.

Conclusion: Tfh elevation occurs in early-stage lung adenocarcinoma and is preserved throughout its progression. The number of Tfh is correlated to the presence of TLOs, the tumour mutational load and the expression of cancer testis antigens. These results suggest that Tfh are involved in mounting an active immune response against tumour neoantigens in LUAD.
PLANNING STUDY: FROM VMAT ON A CONVENTIONAL LINAC TO DYNAMIC-TRACKING IMRT ON VERO – THE IMPACT ON RILD RISK CALCULATIONS FOR HEPATOCELLULAR CARCINOMA OF THE LIVER


Category: Biology/Informatics

Purpose/Objectives: Our institution has been treating hepatocellular carcinoma (HCC) liver patients with Varian TrueBeam volumetric modulated arc therapy (VMAT) since November 2013 and is now offering a Brainlab VERO-based tracking program as a treatment option for managing respiratory-induced tumour motion. The purpose of this study was to assess the impact of this change of treatment technique on previously calculated risk estimates for radiation induced liver damage (RILD).

Materials/Methods: 10 HCC liver patients previously planned with Varian Eclipse treatment planning software (TPS) for VMAT delivery were anonymized and re-planned with Brainlab iPlan TPS for a static-field IMRT dynamic-tracking technique. 7 out of 10 plans were originally planned/treated with a motion-encompassing ITV (internal target volume) method and the remaining 3 plans were planned/treated with a gated VMAT technique. The PTV for the TrueBeam VMAT plans was generated by adding 5 mm to the CTV (for gating method) or ITV (for motion-encompassing method). For the dynamic tracking re-plan, PTV contours were created by adding a uniform margin of 8 mm from the original GTV contour. This margin was chosen based on literature recommendations for dynamic-tracking. Each dynamic-tracking IMRT re-plan aimed to dosimetrically match the original VMAT plan in terms of PTV coverage, organ-at-risk (OAR) constraints, as well as a calculated RILD risk level (accept < 5%). The RILD risk level was calculated using known Lyman-Kutcher-Burman NTCP model parameters (n = 0.97, m = 12, TD50 (primary cancer) = 39.8 Gy) and was generated from DVH data exported from iPlan using in-house MATLAB code. Tumor motion was also recorded for all ITV VMAT plans in order to explain RILD differences. Finally PTV volume and RILD were compared for all plans.

Results: Tumor motion ranged from 1.0 to 1.5cm in ITV VMAT plans. PTV dose coverage requirements and OAR constraints were all met using the IMRT dynamic-tracked technique. All PTV contours in the dynamic-tracked plans resulted in reduced volumes compared the treated VMAT volumes with an average reduction of 43 cm^3 (reductions ranging from of 4 to 104 cm^3). The risk of RILD was reduced in 8 out of 10 plans (percentage point reductions ranging from 0.3% to 10.5%) while an increase in RILD percentage point of 0.1% occurred in the remaining 2 plans. For all 3 TrueBeam gated VMAT plans, the new dynamic-tracking technique resulted in a reduction in the calculated risk of RILD.

Conclusion: All VERO-based IMRT dynamic-tracking plans met our current TrueBeam VMAT technique dosimetric constraints. Implementing a dynamic-tracking technique will reduce PTV volumes and RILD risk factors for patients with respiratory motion as low as 1cm.
Background: Inactivation of tumor-suppressor ARID1A is prognostic in a number of malignancies. Almost 50% of clear cell ovarian carcinomas (CCOC) and 30% of endometrioid ovarian carcinomas (ENOC) have a loss of function (LOF) mutation in ARID1A; however, there are contradictory reports regarding its clinical value in ovarian carcinomas. We investigated associations between ARID1A mutations and prognosis, DNA mismatch repair deficiency (dMMR), and immune cell infiltration in CCOC and ENOC.

Design: Tissue microarrays with 1,024 ENOC and 595 COCC from the Ovarian Tumor Tissue Analysis consortium, and the TFRI-Canadian Ovarian Experimental Unified Resource, were analyzed for ARID1A loss as a surrogate for LOF mutation. Subsets were analyzed for dMMR and correlated with data on CD8 TIL. Quantitative analysis of TIL (CD3/CD8), B/plasma cells (CD20/CD79), and macrophage/immune checkpoint pathways (CD68/PD1/PDL1) in tumor and stromal fractions is ongoing using multi-color IHC.

Results: ARID1A expression was negative in 41% of CCOC and 24% of ENOC (24%). ARID1A negativity showed no correlation with outcome or stage in CCOC (p=0.65) or ENOC (p=0.77). CD8 TIL were present at some level in 53.5% of CCOC and 74% of ENOC with loss of ARID1A expression, however the number of CD8 TIL did not correlate with ARID1A status (p=0.4086 and p=0.9482). Loss of MMR proteins in ENOC showed a strong association with ARID1A loss (p=0.0006). Finally, ARID1A loss in CCOC correlated with an increase in CD68+/PDL1+ macrophages (M2-phenotype) in the tumor epithelium and stroma (p= 0.0004 and 0.0006 respectively), whereas ARID1A wildtype CCOC appeared to be enriched for CD68+/PDL1- (M1 phenotype) in tumor epithelium (p= 0.0312).

Conclusion: In contrast to prior, smaller studies, we found no evidence that ARID1A status is prognostically significant in either CCOC or ENOC. Similar to reports in endometrial and gastric cancers, we observed association between ARID1A loss and dMMR amongst ENOC. Lack of association between CD8 TIL and ARID1A mutation status suggests ARID1A status may not influence CD8 TIL mediated anti-tumor immunity, and alternative immune populations may play a more critical role in tumor progression. Consistent with this our preliminary analysis of macrophage populations suggests ARID1A loss may influence an anti-inflammatory microenvironment and additional study of immune markers is warranted.

This project uses data from the Terry Fox Research Institute’s Canadian Ovarian Experimental Unified Resource.
GENETIC PROFILING OF DIFFUSE LARGE B-CELL LYMPHOMA USING A SUITE OF DROPLET DIGITAL PCR ASSAYS TARGETING MUTATION HOTSPOTS


Category: Biology/Informatics

Providing timely, cost-effective and accurate genetic testing is one of the most urgent demands in the growing field of personalized medicine. Droplet digital PCR (ddPCR) is emerging as one of the most promising molecular techniques for the rapid genetic interrogation of clinical specimens, including non-invasive liquid biopsies and other low-quality samples. In diffuse large B-cell lymphoma (DLBCL), patients are uniformly treated with frontline R-CHOP therapy despite the strong association between prognosis and known molecular subgroups. The development of assays to genetically stratify DLBCL patients is therefore paramount. Here, we demonstrate the utility of novel multiplex ddPCR strategies for the detection and quantification of a substantial fraction of the complex repertoire of somatic mutations that characterize DLBCL tumours. Our probes target 24 common DLBCL mutation hotspots, some of them strongly associated with either the more aggressive activated B-cell subtype (e.g. MYD88 L265P, CD79B Y196 or NFKBI3 3'UTR) or the prognostically favourable germinal centre B-cell subtype (e.g. EZH2 Y641 or MEF2B D83). We have validated 124 single nucleotide variants and indels by leveraging 23 wild-type specific and 2 mutant-specific hydrolysis probes that can be flexibly distributed in dual-locus, triple-locus or even quadruplex assays. Our suite of ddPCR assays has the potential to detect at least one somatic event in 68% of DLBCL patients from our validation cohort (N=340) and can identify high-risk patients expected to respond to second-line ibrutinib therapy in the refractory/relapsed disease setting.
97. DNA METHYLATION PROFILE AS A DIAGNOSTIC TOOL FOR THYROID NODULES

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Presenting author is a post-doctoral fellow.

Category: Biology/Informatics

Background: The differential diagnosis of thyroid lesions using fine-needle aspiration (FNA) is a challenge. The increased worldwide incidence of thyroid cancer and the indications of FNAs have resulted in a large number of patients that undergo diagnostic surgery and, in many cases, this procedure is not necessary. Molecular tests for the detection of epigenetic changes associated with malignancy are a potential tool for the diagnosis of thyroid carcinomas. We aimed to develop a diagnostic method for thyroid cancer using DNA methylation analysis.

Study design: A large-scale DNA methylation data previously generated by our group (Illumina 450k) were reevaluated. The epigenomic profile of papillary (PTC=60) and follicular (FTC=10) carcinomas were compared with normal thyroid tissues (NT=50) and benign thyroid lesions (BTL=17). The findings were confirmed using a cross-validation analysis with public databases (GEO and TCGA). Two classifiers (Support Vector Machine method) were constructed to differentiate FTC and PTC. Aiming to increase the applicability of the method, selected differentially methylated CpGs were evaluated by pyrosequencing after DNA bisulfite conversion (PYRO-BIS) in 143 tumors (86 microarray-independent) and 58 BTL samples (array-independent).

Results: Differentially methylated CpGs were identified in PTC (2,130 probes) and FTC (21 probes) compared with NT and BTL. Three probes for each thyroid malignancy (FTC and PTC) were confirmed by external data with the highest diagnostic potential (large areas under the ROC curve). These probes were further selected to train the FTC/PTC-classifier, whose combination achieved 92.9% sensitivity (65/70 FTC+PTC) and 82.4% specificity (14/17 BTL). The PYRO-BIS analysis was executed, confirming a similar performance (90.9% sensitivity and 79.3% specificity).

Conclusions: A thyroid cancer diagnostic tool based on DNA methylation was developed with great applicability and performance.
98. PUTATIVE NOVEL MICRORNAS DISCOVERY IN NON-NEOPLASTIC AND NEOPLASTIC THYROID TISSUES

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Presenting author is a post-doctoral fellow.

Category: Biology/Informatics

Background: Papillary thyroid carcinoma (PTC) is the most common tumor of the thyroid gland and represents one of the largest increases in incidence among all cancers in the last three decades. Diagnostic limitations and the inability to accurately discriminate between indolent and aggressive tumors represent the major challenges in thyroid cancer. MicroRNA (miRNA) are a category of small non-coding RNA which regulate gene expression by direct binding to complementary sequences in their target mRNA. MicroRNAs are frequently disrupted in many cancer types, present high tissue-specificity and molecule stability, thus they are suitable candidates to be used as biomarkers and drug targets. Although approximately 2,800 mature miRNAs have been described to date, we hypothesize that there are additional miRNAs not included in the current miRNA annotation that are tissue/disease specific. Here, we aim to uncover potential new miRNAs in the thyroid and exploring their role in PTC using publicly available datasets.

Methods: Raw small RNA sequencing and clinical data from PTC (n=504) and adjacent non-neoplastic (n=59) samples were retrieved from TCGA database. The data processing and novel miRNA prediction were carried out by the miRMaster online tool (based on miRDeep2.0 algorithm). Matched tumor and normal samples (n=59 pairs) were compared using paired t test (BH corrected P<0.05). The mRNA targets were predicted by miRanda v3.3a algorithm and the targets (regulated by at least 25% of the discovered miRNAs) were submitted to an in silico pathway analysis by miRDIP (BH corrected P<0.05). The putative novel miRNAs were associated with clinical pathological features (unpaired t test P<0.05).

Results: Of the 234 putative novel miRNAs in thyroid tissues from TCGA, 92 were exclusively observed in non-neoplastic and 17 in tumor tissues (125 shared by both sample groups). Most of them (n=152) were differentially expressed in PTC compared to NT (136 under and 16 overexpressed in PTC). A pathway enrichment analysis comprising the predicted target mRNA revealed an overrepresentation of RNA polymerase II transcription (P=0.001) and generic transcription pathways (P=0.006), suggesting a broader role of these miRNAs in gene expression control. Moreover, many disrupted miRNA were associated with more aggressive disease, as advanced primary tumor stage, lymph node involvement and aggressive histological subtypes (tall-cell variant), which might represent a biological relevance of these candidates.

Conclusions: Our results suggest the existence of previous uncharacterized miRNAs in thyroid tissues, which can be related to carcinogenesis and tumor progression with a potential use as biomarkers.
Segmentation is the method of identifying and delineating objects of interest in an image. In this case we tackle segmentation of nuclei within tissue in which cell clusters that contain at least 100 nuclei from digital pathology images. The overlapping of these nuclei makes it difficult to identify their boundaries and isolate them from the larger cluster. In the method presented here we combine multiple stages, each step improving the delineation of nuclei within a cluster. The first step is the creation of the mask of the cell cluster using some form of intensity thresholding. After getting the mask which outlines the cluster nuclei, it is sent through a segmentation process which involves searching for inflection points on the object boundary and separating areas of the cluster by drawing lines between the most appropriate pairs of inflection points. To improve the accuracy of these subdivided nuclei, the next stage is to pass the segmented nuclei and its partial boundary to another process that will fit the nuclei boundary (excluding the just part that was drawn between inflection points to an ellipse and extrapolate from the boundary the rest of the cell edge). Due to the limitations of these processes, the nuclei will still have areas on its boundary that do not follow the true edge of the cell. To improve this, the final step is to do an elliptical transform of the image for each nuclei that will look at the current boundary of the nuclei and improve the boundary by analyzing the balance between the intensity gradient of the image and the curvature of the boundary. In future, we will evaluate if this method improves the quality of nuclei isolation, resulting in improved identification of cancer cells.
100.  A PILOT STUDY OF SMALL GROUP GENETIC COUNSELLING IN AN UNSELECTED PANCREATIC CANCER COHORT

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Category: Population Health/Health Services

Background: In light of emerging treatment utilities from germline genetic information, new service delivery models are needed to increase access to genetic testing (GT). As part of a study offering clinical multigene panel testing to unselected patients with pancreatic ductal adenocarcinoma (PDAC), we piloted small group counseling (GpC) in a subset of participants.

Methods: Eligibility criteria for GpC were a confirmed diagnosis of PDAC and ability to speak English. GpC is scheduled once per month, lasts 60 minutes and involves up to six patients and their support persons. Patients were offered a research-funded clinical grade 30-gene hereditary cancer panel. A patient satisfaction survey was completed at the end of the appointment.

Results: 54 patients attended GpC with an average age of 62.1 (range, 37-84). 67% of patients were female. 16 patients attended GpC by video-conference (n=8) or telephone (n=8) due to geography or poor health status. The majority of patients consented to GT (80%, n=43). Patients who attended GpC in person were more likely to consent to GT than those who attended by telephone or by video-conference (p < 0.01). A history of smoking was inversely correlated to testing uptake (p < 0.01). Six pathogenic variants (PV) were detected in 5 patients (13%) in the genes ATM, BRCA2, MITF, MUTYH (mono-allelic) and one patient with a PV in both ATM and BRCA2. The wait time for patients attending GpC (M=45 days, SD=43) was significantly shorter (t=-2.141, p=0.03) compared to an individual GC appointment (M=63 days, SD=66). Among 32 completed patient satisfaction surveys, the majority of patients indicated that GpC was helpful to them (97%), it increased their understanding of hereditary cancer (88%) and enough time was provided (97%).

Conclusions: Preliminary findings demonstrate high levels of satisfaction and shorter wait times for patients attending GpC. The lower uptake of testing for patients who attended GpC by videoconference or telephone suggests that patients living in remote areas or with poor health status may be better served by standard individualized appointments. Data collection is ongoing. Results will inform future directions for general service delivery; in particular if GT for all PDAC patients is to become widespread.
X-INACTIVATION SPECIFIC TRANSCRIPT (XIST)-MEDIATED MIRNA SEQUESTRATION IN NSCLC

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Category: Biology/Informatics

Background: Long non-coding RNA (IncRNA; >200nt) transcripts have been recently recognized as crucial regulators of gene expression. An emerging mechanism of IncRNA-mediated regulation in cancer biology and therapeutics is their “sponging” of miRNAs, in which IncRNA promote the upregulation of canonical miRNA-target genes. XIST is a prototypical IncRNA involved in cis-silencing of an X chromosome in females; however, in cancer there are conflicting reports of additional impacts on protein-coding genes by sponging singular inhibitory miRNAs. XIST-associated sex-specific differences afford the opportunity to study IncRNA sponging systems within a cancer type. Existing studies considering one miRNA and XIST expression in singular cancer types do not account for important biological considerations including sex and localization of miRNA and XIST transcripts. Here, we detail an in-depth and unbiased pipeline for the discovery of candidate miRNA and gene targets in IncRNA sponging, and validate the miRNA that may be mediating these interactions in XIST.

Methods: We performed a comprehensive analysis of the role of XIST in the positive regulation of protein coding genes using male and female lung adenocarcinoma (LUAD) samples as a model. To find genes regulated by XIST-mediated miRNA sponging, we correlated all Ensembl-annotated genes with XIST expression in female LUAD (n=307; rho>0.4, p<0.05). Using a specialized algorithm based on binding energies and sequence homology, we assessed the potential binding of all miRNAs against target genes and XIST. We then determine the best candidates for sponging by XIST using XIST-high (female and male) and XIST-low (male) systems, and validate the presence of these candidate miRNAs in the nucleus.

Results: Our analysis yielded 543 genes that may be defended from miRNAs by XIST (DMX), with a predicted 804 miRNAs targeting both DMX genes and XIST. We compared the changes in miRNA-DMX relationships in XIST-high and XIST-low systems and discover a high-confidence set of 13 miRNA-DMX gene pairs. Interestingly, 5 of these miRNA-DMX gene pairs involve miRNA with validated nuclear localization.

Conclusion: A massive number of IncRNA sponging studies exist, but most only consider one miRNA in a singular type of cancer, are biased in their selection of this target, and are limited in biological context. By analyzing the transcriptome of female and male LUAD, we identify potential DMX genes and show that the XIST-miRNA-DMX sponging axis is affected by expression of sex-specific genes and number of shared miRNA binding sites on DMX genes. Importantly, we identify that the miRNAs that mediate the XIST-DMX gene axis are enriched in the nucleus, co-localizing with XIST. In summary, our analysis provides both a comprehensive methodology for studying cancer-related miRNA sponge IncRNAs, and suggests the relevance of XIST to lung cancer biology.
The vision is for cancer care in British Columbia (BC) to be delivered in a coordinated, efficient manner, governed through effective partnerships between BC Cancer and the Regional Health Authorities (RHAs). In early 2017, BC Cancer in partnership with the RHAs identified that the increased need for outpatient medical oncology services, combined with human resource and healthcare facility constraints required a framework for organizing and delivering cancer care services in BC.

Therefore, in October 2017, BC Cancer and Fraser Health embarked on a process to develop a provincial “Tiers of Service” (TOS) draft framework which outlines the responsibilities and requirements of all healthcare facilities in BC in providing outpatient medical oncology services. By December 2018, a provincial working group with members from BC Cancer and all the RHAs and First Nations Health Authority will finalize, endorse and approve the TOS.

Once this occurs, BC Cancer and the RHAs will complete a Self-Assessment (January 2019) for each site currently providing outpatient medical oncology services to determine their “tier” alignment and ability to meet the responsibilities and requirements at that tier. This Self-Assessment is pivotal as results of the reports (i.e. provincial, regional and local actions) will be utilized to inform BC Cancer and each RHAs 5 year cancer care plan. The TOS Self-Assessment will be repeated every few years to continuously review and renew each sites tier alignment, identify existing gaps and will ensure the long term success of the TOS.

Overall, TOS sets standards and provides clarity for service provision, helps build a capacity plan, plans where resources should be located, measures and monitors performance and improves the quality of the patient experience. Through this, partnerships between BC Cancer and the RHAs have strengthened for joint strategic planning of cancer care services (recently identified as a priority by the Ministry of Health).
103. MOTION MANAGEMENT FOR LIVER STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) – ONE CENTRE’S EXPERIENCE WITH RESPIRATORY GATING VS DYNAMIC TUMOUR TRACKING VS MOTION-ENCOMPASSING (ITV) TECHNIQUES


BC Cancer - Vancouver Cancer Centre

Category: Translational/Clinical

Purpose: Patient and technical factors determine which motion management strategy provides an optimal balance between benefit to the patient and efficiency/complexity of treatment for liver Stereotactic Ablative Radiotherapy (SABR). This study describes options for motion-management at a single institution and determines what patient/technical factors contribute to the multidisciplinary decision-making process when choosing between motion-encompassing ITV (internal target volume) method, respiratory-gating with VMAT (Varian TrueBeam), or dynamic-tumour-tracking with 3DCRT (BrainLab VERO).

Materials and Methods: Forty-five patients had fluoroscopic assessment and liver SABR treatment between July 1, 2017 - March 1, 2018. The decision making-process was reviewed to identify patient-specific and technical (planning/delivery) characteristics that contributed to the selection of treatment modality. All patients had implanted fiducials (FIDs), an imaging surrogate for tumour location and motion.

Results: 33 of the 45 patients (73%) received ITV-SABR, 8(18%) VMAT-Gating, and 4(9%) 3DCRT Dynamic-Tracking. The four categories of patient-specific factors influencing choice of treatment were 1) Tumour: volume and proximity to organs-at-risk, 2) FIDs: shape, location, number, radio-opacity, 3) Respiration: amplitude, regularity and correlation of internal/external motion (with/without abdominal compression), exhale phase in gating window of >2sec, and ability to breath-hold in exhale for >20s, 4) Physical/Social: comfort with holding the immobilized position, MRSA+ status, and language barriers. Machine-specific factors were: compatible planning/delivery techniques (ITV Method=VMAT, static-field IMRT, 3DCRT, dynamic conformal arcs (DCA) / Gating =VMAT / Dynamic-Tracking=3DCRT), and the ability to detect/monitor FID position during treatment. A decision tree was created to guide the healthcare team during a pre-simulation fluoroscopy to select the most appropriate treatment for liver SABR.

Conclusions: All motion-management methods are utilized at this clinic and are necessary to maximize the number of patients eligible for liver SABR. Communication during the decision-making process is multidisciplinary. Each method has specific benefits and limitations and a decision tree can help ensure that lines of communication between health care professionals are transparent and as a result, liver patients undergoing radiotherapy receive the most appropriate treatment.
DISCOVERY OF PREVIOUSLY-UNANNOTATED MIRNAS IN GASTRIC CANCER

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Category: Translational/Clinical

Background: MicroRNAs (miRNAs) are key regulators of gene expression, involved in nearly every cellular process. Primarily, they act by silencing their mRNA targets at the post-transcriptional level through complimentary sequence binding. A common event observed in the development of diseases, including cancer, is the deregulation of miRNAs. Currently, over 2,500 mature miRNAs have been annotated in humans. However, recent studies have shown that many temporal and tissue-specific miRNAs have been overlooked. In this study, we analyzed small RNA-sequencing data from gastric non-malignant and tumour tissues to identify previously-unannotated miRNAs relevant to the development and progression of gastric cancer.

Methods: A total of 444 gastric samples, including 41 paired tumour/adjacent non-malignant samples, collected by The Cancer Genome Atlas (TCGA) were evaluated in this study. Small RNA-sequencing data was analyzed using the online platform miRMaster. This platform performs adapter trimming, quality filtering and read collapsing, followed by the alignment of the reads to the hg38 build of the human genome. Additionally, it predicts novel miRNAs using an algorithm analogous to miRDeep2, a well-established novel miRNA discovery tool. To ensure that the novel predicted species were indeed unique miRNAs, we manually filtered the predictions by number of reads, folding structure and GC content. Assessment of the biological relevance of the novel miRNA candidates was performed through differential expression, target prediction and pathway enrichment analysis.

Results: We discovered 170 novel miRNA candidates expressed in gastric tissue and adenocarcinoma, expanding the gastric miRNA transcriptome by 23.5%. Differential expression analysis revealed 143 novel miRNA candidates significantly deregulated between non-malignant and tumour tissues. From these, 132 miRNAs were found to be upregulated and 11 downregulated in tumours when compared to non-malignant tissue. Interestingly, target prediction and pathway enrichment analysis showed that the novel miRNAs candidates may be associated with gene transcription, highlighting their relevance in the development of gastric cancer.

Conclusions: Overall, we not only expand the miRNA transcriptome in gastric tissues by 23.5%, but also reveal regulatory networks with increased biological relevance for the development and progression of gastric cancer. Therefore, our results will aid in the development of new prognostic and diagnostic tools for the management of gastric cancer patients.
Non-small cell lung cancer (NSCLC) patients that express activating mutation(s) in the epidermal growth factor receptor (EGFR) gene in their tumors qualify for and benefit from systemic targeted treatment with EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib or afatinib. However, these patients will eventually develop resistance to these first- and second-generation EGFR TKIs, with the most commonly identified molecular mechanism of resistance being the acquired mutation T790M in the EGFR gene. Patients with identified EGFR T790M mutations are eligible to receive treatment with osimertinib, a newly approved third-generation EGFR TKI that is specifically designed to covalently bind to the EGFR protein bearing the T790M mutation. Acquired resistance to osimertinib has also been reported, with a tertiary mutation in EGFR C797S being identified as a common resistance mechanism. Previously, the only option available to detect resistance mutations in NSCLC patients being treated with a first-generation EGFR TKI and diagnosed with progressive disease was by tumour re-biopsy. An alternative to costly and invasive, and often unfeasible re-biopsies is the testing of plasma for circulating tumour DNA (ctDNA). To provide patients in BC accessibility to this testing option, we developed, validated and implemented a clinical droplet digital PCR assay to detect the most common EGFR mutations that lead to EGFR TKI therapy resistance. The novel droplet digital (dd)PCR-based assay is designed to detect the two most common EGFR-activating mutations (exon 19 deletions and L858R) to confirm that ctDNA is present in the plasma. A separate multiplexed ddPCR reaction designed to detect the resistance mutation EGFR T790M and/or C797S is also performed and can distinguish T790M-C797S mutations that occur in cis from those that occur either in trans and/or in separate subclonal populations. A total of 18 patients who were enrolled in a Canadian multi-centre study were used for initial clinical validation of the assay. The known activating mutation was detected in the plasma of 14 of 18 patients indicating that most patients were shedding sufficient ctDNA to be detected with the assay. For patients with detectable ctDNA, the assay was able to confirm T790M positive status in 8 out of 9 patients. The assay also detected the T790M mutation in one patient that was previously identified as being T790M negative by tissue testing. Orthogonal testing by NGS of the two discordant results confirmed the results of the ddPCR assay, identifying these as cases of true genetic heterogeneity between collected tissue and ctDNA. For a subset of patients with concordant results we used this ddPCR assay to determine the relative abundance of the activating and the resistance mutations in both tumour tissue DNA and plasma ctDNA. There was good agreement between the ratio of the EGFR T790M mutation to the EGFR-activating mutation in the tissue and plasma for these patients. Finally, the assay was used to detect the acquired mutation C797S in cis with T790M in one patient that developed resistance to third-generation TKI therapy. This test is now available to residents in BC, with a turnaround time of 14 days. This study was funded in part by AstraZeneca and a CIHR grant to AK.
106. DEVELOPMENT OF DAILY AND ROUTINE QUALITY CONTROL PROCEDURES FOR VERO

MENDEZ, C., Luchka, K.

Category: Translational/Clinical

The purpose of this study is to describe the development of the quality control (QC) program for the Vero linear accelerator at BC Cancer-Vancouver Centre. The Vero4DRT system uses a micro-small standing wave guide that produces a 6 MV beam that is collimated by MLC only. This assembly is mounted on a gimbal system that allows the beam aperture to tilt and pan. This device is mounted on a rotating ring-shaped gantry that can also rotate on its vertical axis. The gantry also contains a dual kV X-ray imaging system and an electronic portal imaging device (EPID). The patient couch has longitudinal, vertical and lateral motion axes as well as robotic pitch and roll rotation. We present a QC routine for mechanical performance and dosimetric beam properties, the limitations and challenges presented by this new technology and the methods developed to evaluate these parameters over the last year and a half. We focus on the adaptation of our EPID-based measurements, the development of new software to handle the images generated by Vero, as well as the phantoms developed. The quality control data has been logged with a free machine QC database and the results for output, MLC, gantry, ring and robotics accuracy is evaluated for trends and deviations from manufacturer’s tolerances. The phantoms, methods and software developed have provided useful quantitative data on deviations that have required preventive and corrective intervention.
ENHANCING CANCER-SPECIFIC EXERCISE RESOURCES AND SERVICES ACROSS BRITISH COLUMBIA: THE SUCCESSBC PROJECT

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Category: Population Health/Health Services

Background: Exercise for individuals with cancer is safe and effective at improving many of the adverse side effects of cancer treatments, quality of life and long-term health. The integration of exercise as part of supportive cancer care is an underutilized strategy due to implementation barriers that include cost, space requirements, lack of qualified staff and lack of referral pathways. This has resulted in minimal resources being available to cancer survivors in British Columbia (BC). The aim of the SuccessBC project was to utilize existing resources to expand evidence-informed educational materials and services available to cancer survivors in BC.

Methods: A partnership was established between BC Cancer Patient Experience & Interprofessional Practice, HealthLink BC Physical Activity Services and UBC Clinical Exercise Physiology Lab (CEPL). A provincial model for the standard of exercise delivery was created to guide the implementation of the cancer exercise services within HealthLink BC PAS 8-1-1 telephone line, a provincially accessible service that is delivered by Qualified Exercise Professionals (QEP’s) at no cost to any resident of BC. Research on key barriers and facilitators to exercise service implementation was utilized to inform the model design. Additionally, evidence-informed educational resources within BC Cancer were created and reviewed by key knowledge users, including cancer survivors, healthcare professionals and physicians, prior to being made publicly available.

Results: Between September 2017 and September 2018 four main outcomes were achieved during by the SuccessBC project: 1) Expansion of HealthLink BC services to include Physical Activity Services (PAS) for Cancer, delivered by a QEP with cancer-specific training; 2) Development and integration of a cancer exercise consultation tool that guides work-flow, for use by the QEP within the PAS for Cancer service; 3) Creation of evidence-informed educational resources for BC Cancer, including an Exercise Support webpage and electronic educational resources specific to exercise guidelines during cancer treatments, fatigue and breast cancer; and 4) A referral pathway directly to the PAS for Cancer from a Physician or Nurse Practitioner. The effectiveness of the HealthLink BC PAS for Cancer service is currently being evaluated.

Conclusions: Through utilizing existing provincial services and resources for delivery of health information, barriers to exercise service implementation were reduced. The SuccessBC project successfully implemented sustainable exercise-specific cancer support services, educational resources and a referral pathway accessible to all individuals with cancer within British Columbia.
FACILITATING COMMUNICATION OF GENETIC TEST RESULTS FOR HEREDITARY CANCER SYNDROMES: WHAT ARE THE BARRIERS?

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Presenting author is a post-doctoral research fellow with the Canada Centre for Applied Research in Cancer Control, Cancer Control Research.

Category: Population Health/Health Services

Background: BC Cancer’s Hereditary Cancer Program (HCP) has initiated multi-gene panel testing for patients with suspected hereditary cancer syndromes. The types of information returned to patients may require increased health literacy to understand and communicate with potentially affected family members. Comprehension coupled with accurate information sharing within families has the potential to increase uptake of surveillance and risk-reducing measures, resulting in earlier cancer detection and prevention. This study explores patients’ informational needs related to hereditary cancer testing and identifies barriers and facilitators to sharing genetic findings.

Methods: We conducted twenty-five semi-structured qualitative interviews with individuals who had received genetic test results through the HCP between 2017 and 2018. Interviews were transcribed verbatim and analyzed using a grounded theory approach.

Results: Participants reported multiple barriers to communicating test information with family members. Discussions were difficult for patients without a known family history of cancer, where topics related to cancer risk and genetic testing were unfamiliar to family members. A minority of participants struggled with their moral obligation to inform non-immediate family members of results when they did not feel their immediate family members would relay the information. Some participants reported challenges discussing future cancer risk to younger family members. Despite feeling informed about the implications of their own results, participants articulated a need for guidance about how to communicate results with those who may benefit from increased surveillance.

Conclusion: Our study provides evidence that patients strongly desire a resource that facilitates written and verbal discussions about hereditary cancer testing. These results will directly inform the development of a decision aid that provides patients with information and guidance around communicating genetic test results with family members.

Conflict of interest: None
109. EXPRESSION OF LONG NON-CODING RNAS FROM IMMUNE CELLS IN THE LUNG TUMOUR MICROENVIRONMENT

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Category: Biology/Informatics

The tumour microenvironment is characterized by complex interactions between different cell types, including immune cells that may exhibit pro- or anti-tumour effects. In light of recent advances in immunotherapy, characterizing the landscape of infiltrating immune cells is becoming increasingly important. Sequencing and deconvolution techniques present opportunities to identify immune cell composition of bulk tumour data, including the role of the non-coding transcriptome and its regulation of immune- and tumour-biology. Long non-coding RNAs (lncRNAs; >200nt) are key regulators of cancer biology, as well as fine-level regulation to balance pro- and anti-inflammatory phenotypes; yet, the landscape of lncRNA expression in human immune cells remains unknown. Thus, delineating these multifaceted regulatory networks is critical to cancer immunology, particularly in immunogenic malignancies such as lung cancer.

RNA-sequencing data of purified immune-cell subsets (CD8+ T, CD4+ T, B, Monocytes, Neutrophils, and Natural Killer) obtained from flow-sorted healthy peripheral blood samples were probed for lncRNA expression. Sequencing reads were aligned and quantified, yielding 4919 expressed lncRNAs. LncRNA expression patterns were analyzed and their differential expression in tumours was assessed. These immune-associated lncRNAs were correlated with immune cell infiltrate in tumour and paired non-malignant lung adenocarcinoma samples (n=54, The Cancer Genome Atlas), denoted by leukocytes unmethylation for purity (LUMP) scores.

We observed that lncRNA expression patterns are highly cell-type specific in immune cells, where 676 lncRNAs had detectable expression in only one cell type. Many lncRNAs are differentially expressed between tumour and normal tissue, as well as between tumours with high and low mutation burden. Compared with lung tumour samples, 19 immune-associated lncRNAs were significantly negatively correlated with LUMP scores (r<0.400, BH-p<0.0100), 17 of which were also positively correlated with CD45 gene expression (r>0.400, BH-p<0.0100) suggesting expression from immune rather than tumour cells. For instance, the lncRNA USP30-AS1 is significantly downregulated in tumours (average fold-change=2.96, BH-p=6.88*10^{-13}), suggesting a relevance to tumour biology; however, transcript expression is correlated with decreased LUMP score (r=-0.685, BH-p=1.02*10^{-4}), illustrating its specificity to immune cells.

Here, we present an atlas of cell-type specific lncRNAs in human immune cells. Our data suggest a functional relevance of lncRNAs to the biology of the tumour microenvironment, and the necessary consideration of tumour purity when examining non-coding RNA expression in order to avoid conclusions confounded by immune cells in bulk tumour data. Thus, we provide a resource for further elucidation of genomic links between immune and malignant cells, which may aid the development of future prognostic and therapeutic strategies.
Approximately 35% of patients undergoing colorectal surgery experience post-operative complications, as well as reductions in exercise capacity and physical function. Prehabilitation exercise programs begin pre-operatively and may be effective in reducing post-operative complications and improving physical function during recovery. The purpose of the study was to incorporate patient perspective in developing exercise prehabilitation programming. Patients who underwent surgery for colorectal cancer (n=11), or other major abdominal issues (n=8) from April 2017 to May 2018 at St. Paul’s Hospital in Vancouver, BC were recruited for the study. A trained facilitator conducted three focus groups, which were then coded using thematic analysis. Participants in each focus group were asked about challenges experienced during the pre-operative phase, and their perceptions and preferences around prehabilitation programming. Major patient challenges included lack of motivation to exercise, reduced fitness, and physical changes from previous surgeries. Participants emphasized the importance of tailored exercise programs and exercises specific to recovery. Themes of peer support/mentorship and community-based exercise programming emerged as important considerations for program design. Findings emphasize the importance of understanding the patient experience prior to colorectal surgery. The co-design of exercise prehabilitation programming, whereby patient preferences are integrated can potentially improve patient experiences, recovery, and health outcomes.
111. EXPERIENCE TO DIAGNOSIS FOR PATIENTS WITH ORAL PRE-INVASIVE OR CANCEROUS LESIONS

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Category: Population Health/Health Services

Objectives: Oral squamous cell carcinoma (SCC) has high mortality with a 5-year survival rate of approximately 50% and often presents with late-stage diagnosis. Early detection of precancerous oral lesions is the key to better prognosis. The objective of this study was to characterize patient experiences with oral lesions from identification to diagnosis.

Methods: From 2010, patients diagnosed with high-grade (HGL) or SCC lesions were invited to participate in a self-administered, survey-type questionnaire at the pre-surgical consultation at the BC Cancer Agency. The questionnaire was designed to encompass patient demographics and experiences from lesion identification to diagnosis.

Results: Of the 486 patients identified at pre-surgery appointments, 129 (27%) patients consented and completed the experience-to-diagnosis (ETD) questionnaire which made up the cohort for this study. These patients averaged 62±14 years old, with more males (65%) and 1 to 1 ratio of non- to ever-smokers. Among the lesions, 83 (64%) were self identified (SI) with symptoms, mainly painful ulcers or palpable mass (69, 83%) on the tongue (48, 70%), that prompted only 25 (30%) of them to seek healthcare attention from either general dentists (12) or family physician (13). The other 58 (70%) SI patients first thought to wait for the symptoms to subside, change diet, or improve self-care oral hygiene before seeing any health practitioners (HPs). Among the 129 patients, 46 (36%) had lesions identified by HP that were mostly asymptomatic (40, 87%).

A total of 61 HGLs and 68 SCCs were diagnosed within similar time from identification to diagnostic biopsy. Significantly higher rates of SCCs were SI compared to HP identified (44% vs 24%, \( p = 0.01 \)); while HP detected all asymptomatic HGL (29, 22%) and SCC (13, 19%) lesions. The average time from identification to first examination was 0.8±3.4 months, and there was no difference between SI and HP identified (1.0±4.1 v.s. 0.6±1.1 months, \( p = 0.46 \)). Upon first examination, 79 (61%) were referred to specialists (oral medicine or ear-nose-throat), 18 (14%) had multiple referrals to other general dentists or family doctors, 18 (14%) waited-watched, and 14 (11%) had lesions biopsied. Overall, the time between detection to diagnostic biopsy in BC was over 3 months for 70 (54%) patients.

Conclusions: The study highlights that oral cancer screening by HPs can identify asymptomatic at-risk or cancerous oral lesions. However, patients’ awareness of the urgency in mucosal abnormality is lacking, underlining the ongoing need to promote oral lesion awareness to both patients and community HPs to facilitate earlier diagnostic workup of oral lesions and, subsequently, achieve a better outcome.

112. COMPARISON BETWEEN MACHINE LEARNING AND DEEP LEARNING FOR SUB-CM LUNG NODULE IMAGE CLASSIFICATION

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Category: Biology/Informatics

New clinical challenges have arisen from the recent recognition for an improved mortality of cancers via lung cancer screening using LDCT. A particular challenge for physicians and CADx systems is the classification and prediction of behavior for sub-cm lung nodules that are frequently present in screening CT scans. We have evaluated multiple imaging processing techniques to aid in the CADx of these small nodules such as Radiomic feature-based classical machine learning methods (linear discriminant functions) as well as constructing inhouse convolutional neural networks (CNN) that utilize deep learning methods and leveraging pretrained networks such as VGG16, VGG19, and InceptionV3 for instances of transfer learning. The linear discriminate Radiomic analysis classified a small sample size (n=53 cases) using quasi-volumetric nodule data (images of the nodules from CT slices above and below the central slice) into three discriminate categories: cancerous (clinically confirmed) versus resolved (not present in follow up CT scans) versus stable (a negligible change in shape, texture, size in follow up CT scans). The LDA Radiomic analysis correctly classified the small sample size with an accuracy of 82% using only 3 predefined traditional image analysis features (2 shape features, 1 texture feature). The inhouse CNN trained on this same quasi-volumetric data achieved an accuracy of 78%. The leveraged pretrained networks VGG16, VGG19, and InceptionV3 trained using bottlenecking and finetuning resulted in an average accuracy for classification of 76%, 82%, and 72% respectively through 4 crossfold validation. These results suggest the implementation of a modality-bridging techniques to acclimate the pretrained networks from the “natural” image domain to the medical image domain (CT scans) can be successful on limited training sets provided the set specific training is limited to optimizing the higher level features of the CNN to the characteristics uniquely present in CT nodule data.

This work has been supported by TFRI Project Reference: 1068.
The early detection of cancer brings increased success in the treatment of cancer patients. A prototype sub-millimeter diameter high resolution fibre endoscope for the in-vivo imaging in oral, lung, cervix, ovarian and pancreas sites for the early detection and delineation of cancers is currently in its early stages of development. The endoscope is to utilize a combination of rotary and pullback motion to cover a wide field of view while capturing high-resolution (10 to 20 µm) RGB images. In this system red, green and blue lasers use the core of a dual-clad fibre for illumination and the inner cladding for detection to achieve real time in-vivo reflectance imaging. Signal detection for each laser (RGB) has been tested using a white card printed with black and RGB lines of varying widths. The RGB contrast for black ink on white paper and the Signal to Noise Ratio (SNR) for the pullback mechanism of the system were determined. The contrast values for red, green and blue light were 34.47, 34.53, and 30.15 respectively, and the SNR values were 2700, 2800 and 1000 respectively. An (18 x 5) mm² colour image of a section of the card was composed by directing pullback motion parallel and perpendicular to the probe and by modulating the RGB laser diodes so that the detection could be done with a single detector, further demonstrating the image capturing capabilities of the system. Moving forward, various sections of the prototype endoscope will be rotated and tested to determine the image quality from rotary motion. The imaging performance characteristics of the endoscope with rotary and pullback motion combined will then be further quantified.
114. THE SS18-SSX ONCOPROTEIN IS DIRECTED BY DNA METHYLATION STATE TO EVICT POLYCOMB IN PRIMARY SYNOVIAL SARCOMAS

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TFRI Title: The Terry Fox New Frontiers Program Project Grant in New Vistas on Cancer Biology and Treatment: Conceptual Advancements from the Forme Fruste Project
Project Leader: David George Huntsman

Category: Biology/Informatics

Background: Synovial sarcoma is characterized by a balanced chromosomal translocation t(X,18; p11,q11), resulting in the production of a fusion oncoprotein, SS18-SSX. Recent models based on cell line experiments have proposed that the oncoprotein takes advantage of other complexes, including KDM2B-PRC1.1, a noncanonical polycomb repressive complex, and mammalian SWI/SNF (BAF), a chromatin remodelling complex, to drive this cancer. Specifically, KDM2B binds unmethylated CpG islands (CGIs), recruiting SS18-SSX and BAF, and ultimately activates genes that would be otherwise repressed.

Methods: We have profiled 5 synovial sarcoma primary tumors using a Post-Bisulfite Adapter Ligation (PBAL) protocol for DNA methylation, RNA-seq for transcriptome data, and Chromatin Immunoprecipitation sequencing (ChIP-seq) for 6 core histone modifications (H3K4me3, H3K4me1, H3K9me3, H3K27me3, H3K27ac, H3K36me3). RNA-seq and ChIP-seq were similarly performed on 2 synovial sarcoma mouse model tumors. Publicly-available RNA-seq and ChIP-seq data (histone modifications, KDM2B and SS18-SSX) were obtained for control, SSX and KDM2B knockdowns in the HSSYII and Aska synovial sarcoma cell lines.

Results: Using ChIP-seq datasets from the HSSYII cell line, SS18-SSX and KDM2B showed co-occupancy at their binding sites. These binding sites demonstrated eviction of H3K27me3 in HSSYII control compared to KDM2B knockdowns. However, such a relationship did not hold true in the primary tumors, suggesting SS18-SSX and KDM2B binding sites may vary amongst individual synovial sarcomas. Moreover, previously established synovial sarcoma gene signatures from cell lines were not consistent in the primary tumors. Greater variability was also seen in CGI methylation of primary synovial sarcomas compared to neuroprogenitor cells. KDM2B binding was associated with hypomethylated CGIs in primary synovial sarcomas, and this may define unique SS18-SSX recruitment in each individual tumor. A subset of genes significantly downregulated following HSSYII KDM2B knockdown and targets of SS18-SSX binding showed increased H3K27me3 signal at their promoters in KDM2B and SSX knockdowns compared to the primary synovial sarcomas.

Conclusion: Using primary human and mouse model synovial sarcomas, we integrated models from cell lines that suggest that KDM2B binds hypomethylated CpG islands, and that these regions differ between individual tumors based on their unique DNA methylation states. KDM2B may then recruit SS18-SSX and the BAF complex to evict polycomb and thus activate genes, including bivalently marked genes, which drive tumorigenesis.
The key hematopoietic transcription factor *RUNX1* is recurrently mutated (15% of cases) in T-ALL leading to a reduction of its DNA-binding affinity and ability to associate with DNA binding partners. Such loss of function mutations suggest that *RUNX1* acts as a tumor suppressor during normal T-cell development. However, wild type *RUNX1* can also be overexpressed in T-ALL and a subset of pro-oncogenic NOTCH1 target genes are coordinately regulated by *RUNX1* and NOTCH1 in human and mouse T-ALL. The molecular mechanisms driving the pathogenic transcriptional signatures associated with *RUNX1* alone and in partnership with NOTCH1 are largely unknown. To address this, we knocked down NOTCH1 by pharmacologic inhibition (NOTCH1-KD) and *RUNX1* (RUNX1-KD) by lentiviral shRNAs in a T-ALL cell line (KOPTK1) and performed RNA-seq and ChIP-seq for active (H3K4me1, H3K4me3, H3K27ac, H3K36me3) and repressive (H3K27me3, H3K9me3) histone marks in control and knockdown samples.

We observed a significant loss of H3K27ac density following *RUNX1* knock-down with ~50% of the 52,427 H3K27ac marked regions showing a >= 2-fold loss of H3K27ac density. Genomic regions that lost H3K27ac density were enriched with *RUNX1* and P300 binding sites and associated with genes involved in cell cycle, Notch and other T-cell signaling pathways. 55% (5,895/10,633) of the *RUNX1* and NOTCH1 co-occupied genomic regions showed a gain (>= 2 fold) of H3K27me3 density upon NOTCH1-KD and loss of H3K27ac upon *RUNX1*-KD. This is consistent with a model where *RUNX1* acts in cooperation with NOTCH1 to establish and maintain H3K27ac and NOTCH1 evicts H3K27me3 to drive transcriptional activation of *RUNX1*+NOTCH1 regulated genes. At least 64 NOTCH1 target genes (e.g., HES4, DTX1, MYC etc.) were co-regulated with *RUNX1* through synergistic modification of H3K27 residue. In addition, our analysis revealed a mechanistic link between *RUNX1* and its role in disrupting the G1-S checkpoint by driving expression of CDC25A. Collectively our analysis provides mechanistic understanding of the pro-oncogenic role *RUNX1* in T-ALL.
Shwachman-Diamond syndrome (SDS) is an autosomal recessive ribosomopathy affecting ~1 in 76,000 people. Symptoms include a cumulative risk of leukemia of ~36% by the age of 30 as well as bone marrow failure, pancreatic insufficiency, skeletal abnormalities and cognitive impairment. Around 90% of patients have mutations in SBDS, a highly conserved gene involved in ribosome subunit joining. Given the increase in publicly available data, we set out to identify SBDS homologs and create multiple sequence alignments of sequences spanning the tree of life. In doing so, we identified areas of high conservation that support hypotheses put forward by recent functional studies. We also identified a section of the protein that appears to be missing in archaea, suggesting that the associated process works differently in archaea. Furthermore, our search for sequences also allowed us to confirm the absence of SBDS in bacteria. The SBDS protein product has been described to have three domains. Previous studies have determined domain II to be species specific, yet the exact residues responsible for this species specificity are unknown. Our current research efforts center around identifying the residues that cause this species specificity using machine learning methods based on multiple sequence alignments. Given its associated cancer predisposition, SDS may enhance our understanding of the multi-step progression towards leukemia, as well as shed some light on the association between ribosomopathies and cancer in general.

The authors declare no conflicts of interest.
LYMPH NODES (LNs) ARE THE EARLIEST SITE OF METASTASIS, BUT ALSO SERVE AS HUBS OF IMMUNE RESPONSE DEVELOPMENT AGAINST TUMOR-ASSOCIATED ANTIGENS. ANTI-TUMOR IMMUNOTHERAPY CONTROLS ADVANCED DISEASE IN SOME PATIENTS, BUT SUCH RESPONSES RELY ON THE ESTABLISHMENT OF A PREEXISTING IMMUNE RESPONSE, AND IT IS UNKNOWN WHAT CONDITIONS IN THE TUMOR-DRAINING LN (TDLN) PROMOTE THE DEVELOPMENT OF EFFECTIVE ANTITUMOR IMMUNITY. UPON ANTIGENIC STIMULATION, LYMPHOCYTES PROLIFERATE WITHIN THE T CELL PARACORTEX OR B CELL-RICH GERMINAL CENTERS OF THE RESPONDING LN, WHERE MOLECULAR CUES DictATE THEIR DIFFERENTIATION INTO EFFECTOR OR MEMORY CELL SUBSETS. WE HYPOTHEZIZED THAT REGIONS OF LOW OXYGEN (HYPOXIA) DEVELOPED DURING LYMPHOCYTE EXPANSION IN TDLNs, AFFECTING THE DIFFERENTIATION OF IMMUNE CELLS AND EFFICACY OF ANTI-TUMOR IMMUNITY. USING FLOW CYTOMETRY AND MICROSCOPY, WE FOUND THAT 60% OF MICE BEARING SYNGENEIC 4TO7 MAMMARY TUMORS DEVELOPED HYPOXIA IN THEIR INGUINAL AND AXILLARY LNs, WHILE LNs FROM NAIVE MICE WERE HYPOXIA-FREE. INJECTION OF LETHALLY-IRRADIATED TUMOR CELLS UNDERGOING IMMUNOGENIC CELL DEATH WAS SUFFICIENT TO INDUCE HYPOXIA, WHICH WAS CONFINED TO GERMINAL CENTER REACTIONS. IN LNs DRAINING ESTABLISHED TUMORS, HYPOXIA WAS ASSOCIATED WITH MORE ANTIBODY-SECRETING CELLS (ASCs) RATHER THAN B MEMORY CELLS, DESPITE SIMILAR LEVELS OF GERMINAL CENTERS, SUGGESTING THAT TDLN HYPOXIA PROMOTES PREFERENTIAL B CELL DIFFERENTIATION TOWARDS AN EFFECTOR, ASC PHENOTYPE. IN TDLNs FROM BREAST CANCER PATIENTS, HYPOXIA-INDUCIBLE CA9 WAS SPECIFICALLY OBSERVED WITHIN GERMINAL CENTERS. OUR FINDINGS HIGHLIGHT A NOVEL, CLINICALLY-APPLICABLE ROLE FOR LN HYPOXIA IN THE DEVELOPMENT OF ANTI-TUMOR HUMORAL IMMUNITY, WHOSE DETECTION MAY IDENTIFY PATIENTS WITH A PRE-EXISTING ADAPTIVE IMMUNE RESPONSE AGAINST THE TUMOR.
EXPLORATORY ANALYSIS OF RECURRENT MUTATIONS ASSOCIATED WITH TREATMENT IN METASTATIC CANCERS


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Category: Biology/Informatics

The presence and development of drug resistance mutations are major limitations to the effectiveness of therapies in precision oncology. As such, understanding how the genomic landscape is altered in response to therapies as well as the recurrence rate of these mutations would greatly benefit the therapeutic process. However, a lack of large datasets containing both genomic and therapeutic information have limited advances in this field, with the majority of known resistance mutations being a result of detailed clinical case studies and animal models. Here we present an exploratory analysis of mutations associated with treatment in our initial cohort of 570 patients, one of the largest sets of pretreated tumors with whole genome information. Samples were collected from patients presenting with pretreated advanced and metastatic cancers as part of the Personalized OncoGenomics Program. Whole genome and transcriptome sequencing of the tumor was performed and used to identify somatic single nucleotide variants, insertions and deletions, structural variants and fusions, and copy number alterations. Whole genome sequencing generated from matched peripheral blood samples was used to subtract germline variation. Patients were divided into tumour type cohorts, including breast, colorectal, and lung cancers. Treatment-mutation associations were identified in cohorts with sufficient statistical power. Mutation rates were compared against TCGA to ensure novelty of the genomic alteration. Our approach was able to identify known resistance alterations such as recurring ESR1 mutations and FGFR1 amplifications with aromatase inhibitor treatment, as wells as the T790M resistance mutation in EGFR when treated with EGFR inhibitors. In total, 60 treatment-mutation associations, and 49 treatment-CNVs associations, a majority being previously unreported, arose from the analysis. Of these, a few stand out with strong biological relevance, such as PIK3R1 alterations upon treatment with HER2 inhibitors as well as MED23 alterations in the presence of mTOR treatment. Further biochemical investigation is required to assess the validity of these treatment-mutation associations. Ultimately, our investigation illustrates the power of datasets containing both treatment and genomic information, suggesting for a further pursuit of similar datasets and analyses.
Ovarian Sertoli-Leydig cell tumours (SLCTs) are a rare class of sex-cord stromal cell tumors in young females. It contains testicular elements, Sertoli cells and Leydig cells, and may arise from the rewired differentiation of primordial cells that normally produce granulosa cells in the ovary. We have recently identified somatic mutations in RNase IIIb domain of DICER1, an endoribonuclease crucial for microRNA (miRNA) biogenesis, in more than half of SLCTs with moderately or poorly differentiated histology. DICER1 RNase IIIb mutations impaired IIIb cleavage activity of DICER1 in in vitro cleavage assay, failed to reconstitute the expression of 5p-derived miRNAs in mouse Dicer1-null ES cells and is associated with the global reduction of 5p-derived miRNAs in ovarian SLCT. The miRNA production defect in SLCT correlated with the deregulation of genes controlling cell proliferation and the cell fate, such as aromatase and FGF9, and genes that are validated or putative let-7 targets, such as HMGA2, ARID3A and CDC25A, suggesting that the systemic loss of 5p-miRNA by DICER1 mutations may drive both pseudo-differentiation and oncogenic transformation in the ovary. To further understand these, we have developed a transgenic mouse strain that expresses a Dicer1 RNase IIIb mutation under the control of Cre expression and will determine whether induction of Dicer1 mutation in various developmental stages of mouse granulosa cells will lead to development of tumours resembling human SLCT. In addition, we are introducing DICER1 mutation into normal human granulosa cells, isolated from in vitro fertilization patients, to understand how DICER1 mutation controls differentiation and transformation and to model tumour development. These ongoing studies will provide unique models for better understanding the function of DICER1 mutation in oncogenic transformation and set stages for developing targeted therapeutic strategies for patients carrying DICER1 mutation.
Objectives: The objective of this study was to investigate the clinicopathological variables that underlie observed age-related differences in DTC behavior, and may have the potential to improve the tailoring of surgical treatment and adjuvant therapy.

Methods: Medical records from 941 sequential DTC patients who underwent thyroid surgery at a tertiary care Endocrine Surgical Center (St. Paul's Hospital, Vancouver, BC, Canada) between 2005 and 2017 were reviewed. DTC patient sex and pathological characteristics (cancer size, focality, extra-thyroidal cancer extension (ETE), vascular invasion, histological subtype, completeness of cancer resection), and presence (LNM) and extent of nodal or distant metastases, were evaluated for their relationship with patient age. A multivariate analysis of variance (using JMP 13.0 and R 2.12.0) was performed for dichotomous (gender, extra-thyroidal extension, multifocality, and vascular invasion), trichotomous (lymph node metastasis) and continuous (tumor size) variables.

Results: After exclusion of cases with incomplete data and papillary microcarcinomas, which generally are incidentally diagnosed and have an excellent prognosis, 603 patients made up the final study population. In the study population patient age was normally distributed (median 45.0, 1st quartile 35.0 and 3rd quartile 56.0), and the mean age of women was 45.5 years and 48.0 years for men. The correlations between mean age and ETE (P<10^-5), age and size (p=0.0043) and a negative correlation between age and complete resection (p=-0.0022) were significant.

Conclusions: The worse prognosis observed in older DTC patients is due to increased cancer invasiveness (ETE), increased size, and decreased resectability. Further study of the underlying molecular basis for these differences is important, and could lead to more tailored treatment, and improved outcomes for this common human cancer type.

Keywords: Thyroid Cancer, Age, Prognosis, Metastasis, Papillary Carcinoma
Background: Population-based estimates of cancer survival provide valuable insights into the effectiveness of early-detection strategies and the cancer control system as a whole. Prior studies have documented notable differences in cancer survival across countries and variable improvements in survival over time across countries. The ICBP SURVMARK2 project (http://survival.iarc.fr/Survmark/en/About) was initiated to provide comparable estimates of cancer incidence, mortality and survival across six high income countries (Australia, Canada, Ireland, New Zealand, Norway and the UK) to motivate inquiry into cancer system differences that may contribute to differences in survival. We present preliminary findings from this international study.

Methods: Newly diagnosed cases of cancers of the esophagus, stomach, colon, rectum, liver, pancreas, lung and ovary were obtained from population-based cancer registries in 20 jurisdictions within 6 countries. Cases were included if they were diagnosed between 1995 and 2014; all cases were followed for vital status until Dec 31, 2015. We calculated 1-year and 5-year net survival measures by age, sex, period of diagnosis and cancer type. We further examined the change in net survival from calendar period 1995-99 to 2010-14 by jurisdiction and country.

Results: The analysis included data on 3.8 million individuals diagnosed with cancer over the study period, including 170,000 from the province of British Columbia. While net survival improved over the study period in all countries, even for cancers associated with poorer prognoses and most notably for patients aged under 75. There was variation across the six countries examined in the study. Age-standardized 5-year survival for colon cancers diagnosed in 2010-14 varied across jurisdictions from 56.8 to 73.2 (60.5-68.4 across Canadian jurisdictions); similar survival variation was observed for rectal cancers (60.5 to 72.2) (60.5-68.6 across Canadian jurisdictions). The largest absolute increases in survival (comparing 1995-1999 to 2010-2014) were seen for rectal and liver cancers. Further results will be presented.

Discussion: Although improvements in cancer outcomes are noted for all jurisdictions, the persistent gap in cancer survival across high-income countries observed requires further inquiry. Possible explanations for the variation in survival include cancer system differences (e.g. early detection and clinical management of cancer) or differences in the approach to cancer registration and data collection in different jurisdictions. Further work within this project will explore the extent to which stage and age at diagnosis, but also local cancer registration practices contribute to the observed differences in cancer survival.

Acknowledgements: The authors thank the participating cancer registries, the ICBP programme board and management team, as well as the entire ICBP SURVMARK2 team.

Funding: Canadian Partnership Against Cancer; Cancer Council Victoria; Cancer Institute New South Wales; Cancer Research UK; Danish Cancer Society; National Cancer Registry Ireland; The Cancer Society of New Zealand; NHS England; Norwegian Cancer Society; Public Health Agency Northern Ireland, on behalf of the Northern Ireland Cancer Registry; The Scottish Government; Western Australia Department of Health; Wales Cancer Network.
Optical coherence tomography (OCT) and autofluorescence imaging (AFI) has been reported for in vivo endoscopic imaging. OCT-AF imaging may aid biopsy-guidance applications, diagnosis of neoplastic tissue, and/or aid monitoring disease progression in patients. Motion artifacts in the in vivo imaging make identification of features and structures like blood vessels challenging. Correction of distortions of tissue features resultant from motion artifacts may enhance image quality and interpretation of images. Motion artifacts in pulmonary OCT-AFI images may be estimated from both AFI and OCT images based on azimuthal registration of slowly varying structures in the 2D en face image. In this work, we present a quantitative evaluation of motion correction based on the ground truth image and artificial motion artifacts and its correction using azimuthal en face image registration (AEIR) method. In our previous work, a simulation of motion artifacts for 3D or 2D rotational catheter data and AEIR method for correcting motion artifacts was described. Our simulated artifacts may be applied on a ground truth image with no artifacts to create an image with known artifacts for the quantitative evaluation of performance of the correction methods. Since there might be some non-visible motion artifacts in the original ground truth image, we need to apply the correction method before applying the simulated artifacts. However, there is no guarantee that this process converges to a motion-free scan; also the pre-corrected ground truth image is subjected to the correction method for further quantitative analysis. Here, we present a study for quantitative evaluations on a ground truth image of in silico phantom, NURD phantom, and in vivo OCT and AF images.

We have showed that it is needed to apply a pre-correction method to the original ground truth image before applying the simulated motion artifacts for quantitative evaluation of the correction methods. Motion correction may be achieved by either AEIR_{meanProj} or AEIR_{AF} on in vivo images. The AEIR method allows for correction of motion artifacts along the rotational direction in rotary-pullback 2D and 3D image modalities. It corrects artifacts along the rotational direction using the mean projection of A-lines from en face image, which improves correction compared to using the full A-lines data. The performance of AEIR_{AF} method is enhanced compared to the AEIR_{meanProj} method for images that have strong AF signal because of good contrast structures in the image. The combination of two methods may be complementary when both modalities are simultaneously obtained to combine the effectiveness of each in different parts of the pullback. We have also showed the $r$ and $\bar{D}_{comp}$ metrics may be used to quantitatively evaluate the correction methods. These quantitative analyses on more real data seem necessary for a more complete body of work.
Over the past decades, it has been observed an increase in the incidence of cancer in the population. Studies show that cancer can originate from insults suffered by individuals during the intrauterine life, a condition known as Fetal Programming. The perinatal period is characterized by ability of the embryo/fetus to adapt to environmental changes by altering gene expression by post-transcriptional mechanisms. Recently, we demonstrated that maternal protein restriction promotes prostate carcinogenesis in aging offspring rats; However, there is lack of information on the molecular mechanism involved in this process. Thus, we aimed to identify the microRNAs deregulated in young programmed rats and localize its possible targets associated with prostate carcinogenesis. For this, male Sprague Dawley rats born to dams fed standard diet (17% protein) or low protein diet (6% protein) during gestation and lactation were euthanized on postnatal day 21 and the ventral prostate were processed by next generation sequencing (HiSeq-2500 Illumina) to determine the microRNome profile. We identified 15 altered microRNAs (10 up regulated and 5 down regulated). In silico analysis were performed to identify the prediction of mRNA regulated by both up and down differentially expressed microRNA. These mRNAs were analyzed in the Geneontology to identify their involvement in of proliferation, apoptosis, morphogenesis and oxidative stress pathways. These analyses were performed in the databas CBIOPortal and Survexpress, both databank is about cancer diagnostic. Finally, we observed 2 mRNA up regulated: DNA (cytosine-5)-methyltransferase 1 (DNMT1) and receptor-interacting protein kinase 2 (RIPK2), and 6 mRNA down regulated: Phosphatase and tensin homolog (PTEN), Fibroblast growth factor receptor 1 (FGFR1), Secreted Frizzled Related Protein 1 (SFRP1), clusterin (CLU), FYN, Forkhead box protein O1 (FOXO1) both group of mRNA presents worse prognosis in patients. In conclusion, our results highlight that exist microRNAs deregulated in the programmed offspring that can are regulating important pathways to development of prostate carcinogenesis. So, this regulation may be one of the forms of cancer origin in adulthood, what reinforce the "Gardner hypothesis" that PCa can be sourced from the uterus.
IMPLEMENTING LUNG CANCER SCREENING IN CANADA: EVIDENCE FROM THE PAN-CANADIAN EARLY DETECTION OF LUNG CANCER STUDY

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Category: Population Health/Health Services

Background: High-risk lung cancer screening has favourable cost-effectiveness ratios; making it an attractive intervention for lung cancer control. Relatively little is known, however, about the implementation of lung cancer screening in Canadian health care systems. To investigate key barriers and facilitations for lung cancer screening programs, we characterize screening adherence rates in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) and prepared a budget impact analysis for Canada.

Methods: We retrospectively assessed screening adherence to short-term (first-year) and long-term (year-four) annual screening rounds in the PanCan study and explored association with socio-demographic and screening-specific characteristics with logistic regression models and Mann-Whitney rank sum and Chi square likelihood tests. We did a four-year budget impact analysis using published utilization rates for screening-related and incidental healthcare resources, smoking cessation, opportunistic screening and projected market dynamics for entrant lung cancer treatments in Canada, assuming optimal, (57%) screening participation rates.

Results: The PanCan study screened 2537 participants with a baseline LDCT exam; of these, 2254 (88.9%) adhered to the second annual screening exam and 1,762 (69.5%) adhered to the year four exam. After excluding patients who had a cancer diagnosis or died during follow-up, we found significant associations between the second annual exam adherence rate and increased age, higher baseline quality of life, and former (versus current) smoker status (p<0.05); while variables related to optimal delivery of the intervention—such as the use of screening autofluorescence bronchoscopy, screening centre location and indeterminate baseline exam results—were significantly associated with greater adherence (p<0.05). Adherence to year-four screening exams was positively associated with age, family history of lung cancer, baseline quality of life and prior screening exam adherence (all p<0.05). Non-adherence was significantly associated with participants who had greater than 50 pack-years of smoking history and a lower level of formal education (p<0.05). The budget impact analysis indicates that the incremental program costs for screening an estimated 257,914 eligible, high-risk individuals, would introduce a net $404,820,576 million dollars in national expenditure, over the no-screening comparison. The budget impact was sensitive to the adoption of entrant immunotherapy drugs; program costs would be reduced by approximately 50% provided the stage shift from late to early stage lung cancer is at least as effective as observed in clinical trials.

Conclusions: Implementation strategies should account for the context of decreased participation by individuals who are at the greatest risk of developing lung cancer. Program performance measures should monitor the both the characteristics of participants and stage distribution of screen-detected lung cancer.
A RADIOTHERAPY TREATMENT PLANNING TECHNIQUE FOR SECOND COURSES THAT INCORPORATES COMPLETE ORGAN-AT-RISK DOSE HISTORY

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Category: Biology/Informatics

Introduction: For incidences of second cancers, historical dose delivered to organs-at-risk must be considered when assessing lifetime toxicity risks. Commercial treatment planning systems permit inclusion of a base plan to incorporate such historical dose, but do not provide the ability to alter the dose distribution. Historical dose delivered to the diseased tissues is not relevant for the new prescription, so base plan dose in the vicinity of the second cancer must be ignored with ad-hoc practices such as Boolean contours or phony optimization criteria. We describe a new technique, dose cropping, that permits modified base plans to be used for planning second radiotherapy courses. Dose to diseased tissues now occupied by tumours is excised while organ-at-risk dose history is fully retained.

Methods and Materials: Clinical second radiotherapy courses developed with Varian Eclipse were replanned for nine head-and-neck cancer patients. Clinical courses and replans were compared on the basis of plan conformity, dose heterogeneity, maximum spinal cord and brainstem point-dose, and Lyman-Kutcher-Burman tissue control probability to ensure that replans did not compromise tumour control. All plans adhered to current clinical planning constraints and guidelines. Organs-at-risk did not interfere with diseased tissues in any plan. An open source, cross-platform web application supporting interactive dose cropping was built using the DICOMAUTOMATON framework for the purposes of this study.

Results: Replanned courses employing dose cropping were statistically indistinguishable from clinical second courses in terms of plan conformity, dose heterogeneity, and tissue control probability (p>0.31 in all cases). Replans had reduced organ-at-risk lifetime maximum point-doses in every case (median reductions: -5.2 Gy for spinal cord, -4.4 Gy for brainstem).

Conclusions: Dosimetric history cropping is a valuable technique for second cancer radiotherapy planning. It can lead to reduced lifetime organ-at-risk dose without compromising plan conformity, dose heterogeneity, or tissue control probability. Dose cropping is widely applicable and can be incorporated into planning procedures whenever a base plan can be employed.
126. PALLIATIVE RADIOTHERAPY NEAR THE END OF LIFE FOR BRAIN METASTASES FROM LUNG CANCER: A POPULATION-BASED ANALYSIS

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Category: Population Health/Health Services

Introduction: Brain metastases occur in 10% of lung cancer cases at the time of diagnosis and of all patients with brain metastases, 40-50% has a lung primary. Brain metastases have a major impact on prognosis and quality of life. This population based study investigates the patterns of use for treatment of brain metastases in lung cancer patients who died within 4 weeks of radiotherapy.

Methods: All patients who received radiation therapy in British Columbia for brain metastases between January 1, 2014 and December 31, 2015 were identified. Patient and treatment characteristics were collected. Association analysis and multivariable logistic regression analysis were performed to assess associations between patient or treatment factors and death within 4 weeks of treatment.

Results: In total, 740 individual patients were identified, who underwent a total of 826 courses of radiation therapy to the brain. Of these 740 patients, 11% (n = 92) died within 4 weeks of start of treatment. Associations were found between most investigated factors and death within 4 weeks of treatment. On multivariable analysis, chemotherapy (OR = 0.49, 95% CI 0.27 – 0.87, p = 0.015), radiotherapy with more than 5 fractions (OR = 0.12, 95% CI 0.04 – 0.34, p < 0.001) and age between 70-80 years as compared to age between 60-70 (OR = 0.37, 95% CI 0.14 – 0.96, p = 0.04) are all associated with a lower odds of death within 4 weeks of radiation.

Conclusion: In our study population, 11% of patients with brain metastases from lung cancer are being treated in the last 4 weeks of their lives. Several factors can be identified that are associated with this and might be helpful for physicians choosing for which patients it may be wise to omit radiotherapy for brain metastases, especially whole-brain radiotherapy.

No conflict of interest.
Purpose: Perfusion modeling is a computationally demanding procedure which can take up to several cpu-days depending on the imaging protocol and desired precision. Computational efforts required for kinetic modeling, the computational method underpinning perfusion imaging, is increasing due to increasing image resolutions, greater reliance on imaging for clinical diagnoses, and fast acquisition modes which create thousands of image slices within a single series. In this article we present a novel technique for tracer kinetic modeling that handles non-uniform and sparse temporal sampling, and also provides a level-of-detail mechanism permitting dynamic accuracy and runtime trade-offs. Use of this method could enable dynamic allocation of computational resources, and reduce computational workload when reduced precision is sufficient.

Materials and Methods: An algorithm making use of Chebyshev polynomials and Levenberg-Marquardt least-squares optimization was developed. Forty-three image volumes comprising clinical Dynamic Contrast-Enhanced Computed Tomography data from a prospective study investigating hepatocellular carcinomae were analyzed. Images were collected with sparse temporal sampling. A comparable, optimized method based on linear interpolation and analytical integration was also implemented and compared on the basis of runtime and residual sum of squares (RSS).

Results: 800-cpu days of modeling was performed. Voxels were modeled on average in 1.06s for the (non-Chebyshev) linear interpolation approach. Runtime was reduced for the Chebyshev polynomial implementation at any level-of-detail considered (spanning 0.4-2.0x the number of measurements). Runtime was approximately linear in level-of-detail, ranging from 0.41s/voxel to 0.59s/voxel over the level-of-detail range. The Chebyshev approach median RSS spanned 104-108% that of the linear interpolation approach.

Conclusions: Kinetic modeling using the proposed technique can reduce runtime without substantially impacting model parameter estimation. The technique is also intrinsically efficient; in the liver perfusion clinical data set employed, runtime was reduced 59% with a corresponding RSS reduction of only 8%. 
128. A PROCEDURE FOR GENERATING ISOVOLUMETRIC ORGAN COMPARTMENTS FOR ORGANS-AT-RISK USING PLANNING CONTOURS

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Category: Biology/Informatics

Purpose: Intra-organ radiation dose sensitivity is becoming increasingly relevant in clinical radiotherapy. One method for sensitivity assessment involves partitioning clinical organ-at-risk regions of interest and comparing their relative contribution to patient outcomes. We show that an intuitive method for dividing organ contours, compound (sub-)segmentation, can unintentionally lead to sub-segments with inconsistent volumes, which will bias relative importance assessment. An improved technique, nested segmentation, is introduced and compared.

Materials and Methods: Clinical radiotherapy planning parotid contours from 510 patients were segmented. Counts of radiotherapy dose matrix voxels interior to sub-segments were used to determine equivalency of sub-segment volumes. The distribution of voxel counts within sub-segments were compared using Kolmogorov-Smirnov tests and characterized by their dispersion. Analytical solutions for 2D/3D analogues were derived and sub-segment area/volume were compared directly.

Results: Both parotid and 2D/3D region of interest analogue segmentation confirmed compound segmentation intrinsically produces sub-segments with volumes that depend on the region of interest shape and selection location. Significant volume differences were observed when sub-segmenting parotid contours into 18ths, and vanishingly small sub-segments were observed when sub-segmenting into 96ths. Central sub-segments were considerably smaller than sub-segments on the periphery. Nested segmentation did not exhibit these shortcomings and produced sub-segments with equivalent volumes when dose grid and contour collinearity was addressed, even when dividing the parotid into 96ths. Nested segmentation was always faster or equivalent in runtime compared to compound segmentation.

Conclusions: Nested segmentation is more suited than compound segmentation for analyses requiring equal weighting of sub-segments, and could reduce bias that would confound sub-organ sensitivity assessment.
Glioblastomas (GBMs) account for nearly half of all primary malignant brain tumours and have a five-year survival rate of only ~5.5%. Our understanding of the underlying biology of these tumours and the development of new therapies have been complicated in part by widespread inter- and intratumoural heterogeneity. We hypothesized that single-cell RNA-sequencing (scRNA-seq) could be used to characterize cellular heterogeneity in primary GBM and the extent to which this is represented in relevant disease models. To address this, we first obtained two spatially distinct tissue subsamples from ten primary GBMs and generated patient-derived organoids (PDOs) and neurosphere cultures from these. We then performed scRNA-seq on the primary regional subsamples, 1-3 matched PDOs per sample, and matched neurosphere cultures from a subset of samples. We have obtained sequencing data for 28,949 primary tissue cells, 35,650 PDO cells, and 11,808 neurosphere cells, detecting a median of 2,641 genes per cell. While the most considerable differences in gene expression were between individual tumours, we also identified similar cellular subpopulations across tissue samples, PDOs, and neurosphere lines. Importantly, PDOs derived from the same tissue sample were highly comparable to each other, indicating that replicate PDOs faithfully represent the original tumour tissue. Additionally, cell subpopulations identified in PDOs appeared to be more representative of primary samples than did those identified in neurosphere cultures. Preliminary results thus indicate that we can identify extensive inter- and intratumour heterogeneity in primary GBM samples, and that this is propagated to varying extents in PDOs and neurosphere lines. This study will help evaluate the utility of PDOs as novel model systems for GBM, and may also uncover novel therapeutic targets previously unrevealed through bulk analyses.
Dual-mode endomicroscopy (DME) is a diagnostic tool for early cancer detection. It combines the high-resolution nuclei imaging of fluorescence endomicroscopy (FE) with quantified depth-dependent epithelial backscattering as obtained by diffuse optical microscopy (DOM). Both imaging modalities are acquired as video streams in real-time. We have previously shown that DME can differentiate normal from transformed oral tissue in vivo, but due to the varying thickness of the epithelium in different parts of the oral cavity an optimal system would have site specific thresholds for classifying dysplasia.

In this study we capture video-rate images of FE and DOM from 6 sites within the oral cavity of 25 healthy volunteers (12 male and 13 female), ages 21 to 63. For each volunteer, the probe was placed on the left & right buccal mucosa, left & right lateral tongue, ventral tongue and dorsal tongue. Tools were developed to algorithmically identify in the FE data when image quality was unacceptable, either blurred by excessive motion of the probe, poor contact with the epithelium or the contrast dye was improperly administered, etc. Such tools include image registration between images adjacent in time and power spectrum analyses. This allowed poor FE data and the synchronous DOM data to be filtered out of the video data stream.

A two-way mixed effects multivariate analysis of variance within the remaining DOM data across volunteers & tissue sites is performed, and found that variability was largest between subjects, larger than that between sites which is larger than that within tissue types across sides, with variance between different frames from the same video at each site being smallest. This helps to identify the depth-dependent epithelial backscattering signals that best describe the gradient of epithelial cell density specific to each tissue site, and strongly suggest tissue specific classifiers to identify transformed tissue better than global organ specific classifiers previously developed. In this fashion we can pre-indentify, for each site, the features which will be most sensitive to tissue transformation to include in a CNN classifier for early detection and treatment of cancer and pre-cancer.
Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest types of cancer, with a 5-year survival rate of less than 10%. Clinical challenges include late-stage diagnosis, limited therapeutic options, and a lack of biomarkers that predict treatment response. Over 90% of PDAC cases have oncogenic KRAS mutations, which are notoriously difficult to target. Mutant KRAS activates a tumour glycolytic switch (Warburg effect), subsequently increasing tumour growth and chemotherapy resistance. Recently, high-dose vitamin C (VitC) has been reported to disrupt the Warburg effect in KRAS mutant colon cancer cells. However, the toxicity of VitC and its effect on metabolism in KRAS mutant PDAC cells is not known.

To assess the cytotoxicity of VitC, PDAC cell lines (n=10) with mutant or wildtype KRAS were treated with VitC alone (0-20mM), or in combination with gemcitabine or an antioxidant, glutathione (GSH). Additionally, to explore potential metabolic changes due to VitC, exposed and non-exposed cells were assessed for oxidative stress indicated by luminescence using the GSH/GSSG-Glo Assay.

We identified two cell lines sensitive to VitC-induced cytotoxicity: MIAPaca2 (EC50=0.96mM) and Panc1 (EC50=1.78mM), at doses that showed no toxicity in non-cancerous cells, while other cell lines showed reduced or no response. These highly-sensitive cells, which were previously subtyped as glycolytic, had a higher VitC EC50 (MIAPaca2=1.58mM, Panc1=1.98mM) when cultured in low-glucose media, suggesting that cell glucose utilization influenced VitC response. We observed lowered levels of GSH after VitC exposure, indicating increased oxidative stress. Moreover, when GSH was added with VitC, cells experienced no toxicity, suggesting that toxicity occurs by decreasing cellular GSH.

Together, our results indicate that VitC-induced cytotoxicity may be mediated by metabolic alterations including glucose utilization and GSH activity. Knowledge of molecular and metabolic signatures associated with VitC sensitivity will allow us to identify a subset of tumours that may benefit from VitC-based therapeutic strategies.
PAPILLARY FEATURES IN THYROID NODULES WITH AN ATYPIA OF UNDETERMINED SIGNIFICANCE OR FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE DIAGNOSIS INCREASES CANCER RISK AND SHOULD INFLUENCE TREATMENT

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Category: Translational/Clinical

Introduction: The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) is a standardized method that pathologists utilize for reporting thyroid fine needle aspiration biopsy (FNAB) cytology, allows for preoperative risk of malignancy (ROM) estimation, and influences extent of surgery. The objective of this study was to evaluate the influence of papillary features on ROM within the Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS-FLUS) BSRTC diagnostic category.

Methods: A Retrospective review of the records of all individuals undergoing preoperative FNAB and thyroidectomy, between 2010 and 2016, at a single high volume hospital, was carried out. Those cases with an AUS-FLUS diagnosis were identified and sub-classified based upon the presence of papillary features.

Results: For the entire study population of 427 cases there were 93 cases (22%) that had an FNAB AUS-FLUS diagnosis. The overall risk of malignancy for the AUS-FLUS category was 32%. Papillary features were identified in 44 FNAB specimens (47% of the AUS-FLUS cases or 10% of the entire study population) and had a 45% ROM. The 49 FNAB specimens (53%) that did not exhibit papillary features had a significantly lower ROM (20%) (p=0.0069).

Discussion: The presence of papillary features in a thyroid FNAB with an AUS-FLUS diagnosis is common, and is associated with a higher ROM then is currently suggested by the BSRTC. Preoperative patient counselling and extent of surgery should be influenced by the presence of papillary features.
**Who are we:** The current Operational Department is made up of a Director, Project Managers, Clinical Informatics Business Lead, and Clinical Informatics Specialists. There is additional BC Cancer staff and contractors who are associated with the Department to help support the CST implementation i.e. BC Cancer’s CST Implementation Director, CST Adoption Leads & Coordinators, Project Managers and Business Analysts. The department is provincial and supports all BC Cancer centres in the use of the numerous technology solutions in BC Cancer’s environment.

**Why is Clinical Informatics important:** The BC Cancer strategic roadmap includes providing patient-centric care. This will require enhanced technology based solutions. The Clinical Informatics Department supports BC Cancer’s strategic roadmap by providing a planned approach to the selection, implementation and sustainment of technology based solutions.

**What we do:** Clinical Informatics provides leadership and insight to the selection, configuration, training, implementation and optimization of innovative information technologies of BC Cancer to support cancer care and research. Collectively we establish collaborative partnerships with clinicians, researchers, patients and staff to facilitate this work.

**Who we are not:** We are not part of IMITS or Tech Services. While they bring the IT and technical support, Clinical Informatics works alongside these services to apply a business and clinical lens and help bridge between the two. Clinical Informatics supports how the system is used.

**Future Plans**
- Implementation and sustainment of Cerner
- Implementation of patient portal
- Development of a Virtual Health Strategy