Detection of *Porphyromonas gingivalis* in Oral Squamous Cell Carcinoma

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INTRODUCTION :

A link between chronic inflammation and cancer is well-established. For example, an association is observed between irritable bowl disease and colorectal cancer as well as between hepatitis and hepatocellular carcinoma. Periodontal disease is the most prevalent disease of the oral cavity and is characterized by inflammatory mediated destruction of the tissues that surround and support the teeth. Destructive inflammatory processes are initiated by specific bacteria in the subgingival biofilm, including *Porphyromonas gingivalis*. This organism can modulate host epithelial cell pathways that impact apoptosis, cell proliferation and the epithelial mesenchymal transition. *P. gingivalis* can thus impact host cells and inflammatory processes in a manner conducive to the development of oral cancers such as Oral Squamous Cell Carcinoma (OSCC). In order for P. gingivalis to play a role in the etiology of OSCC, it should be physically present in the relevant tissues and thus we sought to examine the presence *of P. gingivalis* in OSCC tissues by fluorescent antibody staining.

OBJECTIVES

This purpose of this study is to determine the presence or absence of *Porphyromonas gingivalis* in oral squamous cell cancer biopsy samples.

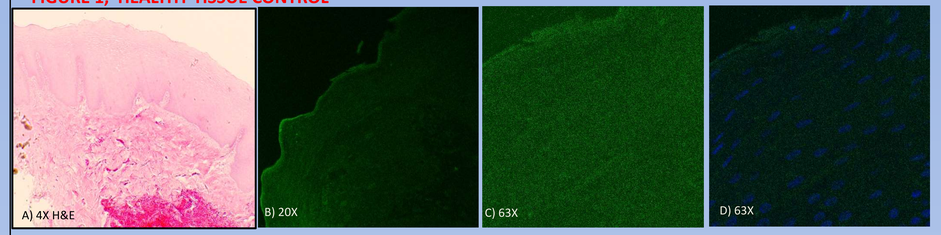
METHODS:

In this study twenty-two oral squamous cell carcinoma samples were subjected to immunohistochemistry in order to detect the presence of *Porphyromonas gingivalis.* The samples included a range of histological grades of SCC ranging from well differentiated, moderately differentiated, and poorly differentiated. The tongue is one of the most common sites of OSCC and the majority of samples analyzed were tongue samples. Gin+gival SCC is much more rare, but five of those samples were included since *P. gingivalis* shows a propensity for gingival tissue. One non-cancerous sample was used as the control tissue. A rabbit polyclonal antibody against *P. gingivalis* (1:1000) was applied to all samples followed by a fluorescent secondary antibody (Alexa-Fluor 488. 1:500). Samples were counterstained with DAPI in order to visualize the nucleus. The negative control used was a rabbit polyclonal antibody to *Streptococcus gordonii* (1:1000). All samples were mounted with ProLong gold mounting media and visualized with confocal microscopy (Leica SP8).

DISCUSSION:

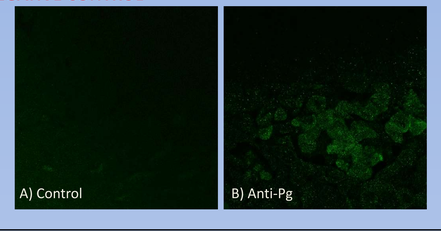
Patients with chronic periodontal disease have an oral cavity environment that is chronically inflamed. There is a clear association with chronic inflammation and cancers as seen in hepatitis and hepatocellular carcinoma. It has been demonstrated that *P. gingivalis* can increase epithelial cell migration. That fact combined with the results of this study showing the presence of P. *gingivalis* in OSCC tissues, indicate that *P. gingivalis* could predispose a patient to cancer or may actually worsen cancer progression.

FIGURE 1, HEALTHY TISSUE CONTROL



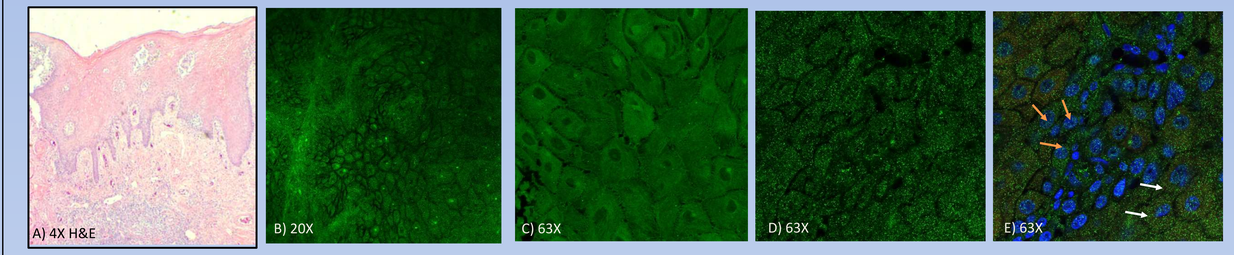
A) H&E Stain of fibroma samples showing normal epithelial tissue architecture B) 20X image of fibroma tissue stained with anti-Pg antibody showing a lack of staining C) Higher power image confirming negative staining D) Higher power image with DAPI overlay to visualize nuclei within cells

NEGATIVE CONTROL



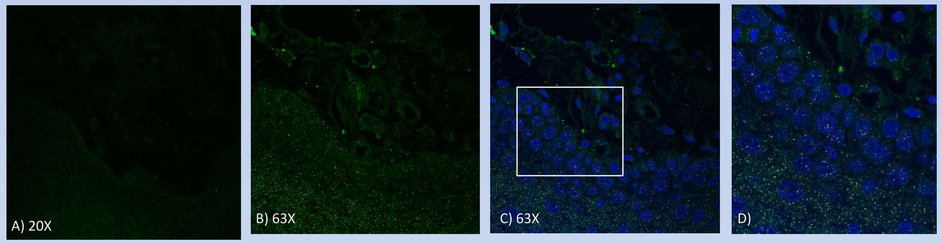
A) This is a higher power image of gingival SCC tissue that was stained with anti-*S. gordonii* antibody. This sample did not show any staining for the organism B) The same biopsy sample was subjected to anti-Pg and shows punctate staining

FIGURE 2, WELL DIFFERENTIATED CARCINOMA



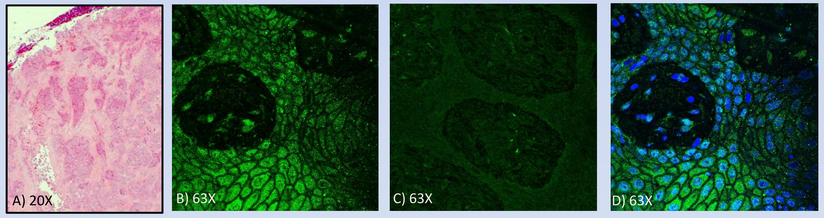
A) Lower power image of well differentiated SCC stained with H&E B) Lower power image of the same sample stained with anti-Pg antibody (1:1000) C) Higher power of the no antibody sample showing a clear lack of staining D) Higher power of anti-Pg showing distinct punctate staining throughout the cells. E) anti-Pg (green) with DAPI nuclear stain and also pan-cytokeratin antibody label for epithelial cells (red). This shows that the organisms are distributed throughout the tissue with nuclear and cytosolic presence of Pg (orange arrow = nuclear, white arrow = cytosolic)

FIGURE 3, MODERATELY DIFFERENTIATED CARCINOMA



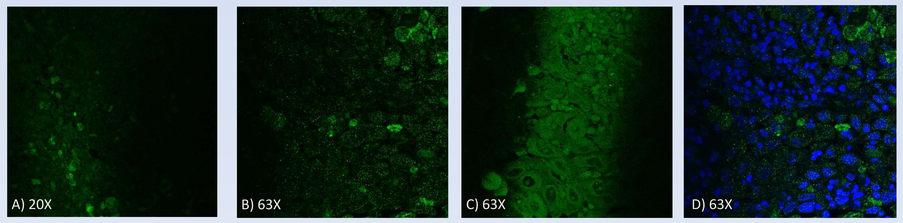
A) Lower power image of anti-Pg labelled moderately differentiated carcinoma, not easily seen B) Higher power showing dots of Pg staining C) Pg with DAPI overlay showing both nuclear and cytosolic location of Pg D) Larger image of cells showing a high number of organisms within the cells

FIGURE 4, POORLY DIFFERENTIATED CARCINOMA



A) Low power H&E stained poorly differentiated carcinoma B) Higher power showing bright green staining of Pg especially in the parenchyma of the tumor C) Higher power of the same sample, but without any primary antibody. D) anti-Pg with DAPI nuclear stain

FIGURE 6, GINIGIVAL SQUAMOUS CELL CARCINOMA



A) Lower power of gingival SCC stained with anti-Pg B) Higher power stained with Pg showing small green dots indicating presence of Pg. C) Higher power of sample without primary antibody D) Higher power Pg with DAPI nuclear stain

TABLE 1, SUMMARY OF RESULTS

Grade	Positive *P. gingivalis* staining
Carcinoma In Situ	2/2
Well Differentiated	3/3
Moderately Differentiated	2/3
Poorly Differentiated	7/8
Gingival SCC	5/5

CONCLUSIONS:

- There are detectable amounts of *Porphyromonas gingivalis* in oral squamous cell cancer biopsy samples take from two areas, the tongue and the gingiva
- *P. gingivalis* is observed both in the nucleus and the cytosol of tumor parenchymal cells
- *P. gingivalis* may be contributing to cancer progression by maintaining an inflammatory environment or impacting the signaling that controls cell life/death

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Quality of Life Assessment for Patients Undergoing Irreversible Electroporation for Treatment of Locally Advanced Pancreatic Cancer

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Abstract

Background: Irreversible electroporation (IRE), is a new surgical, non-thermal based ablative modality that has been shown to be safe and efficacious, however concerns remain regarding short and long term quality of life (QOL) effects of this procedure. The objective of this study is to evaluate the quality of life (QOL) before and after IRE therapy for treatment of locally advanced pancreatic carcinoma (LAPC). The hypothesis for this study is IRE of LAPC leads to short term (6-12 week) adverse QOL effects, but normal or better long term (>6mon) QOL effects.

Method: An IRB approved prospective evaluation of the QOL effects from IRE therapy to treat LAPC from November 2012 to December 2015 was performed. The QOL questionnaires (EORTC QLQ-C30 V2.0) was administered before surgery and 1,3 and 6-month after surgery. Descriptive statistics, one-way ANOVA and effect size calculations were used in analysis of the 15 modules.

Results: Forty-two patients were enrolled (19 male, 23 female) with median age of 59 years (range 27- 75). The global health status scale was lower at 3 months and normalized at 6 months with large effect size (ES) of 0.96 at 6 months (p=0.001). The symptom scales constipation and insomnia showed higher averages at 3 months (p=0.007 and p=0.003 respectively), while dyspnea had higher average at 6 months (p<0.001) (ES of 1.18). Finally, changes were noted in the diarrhea symptoms scale at 1 and 3 months (p<0.001) with ES of 1.24 at 3 months.

Conclusion: Patient perceived symptoms last longer than functional issues. The overall QOL improved after 3 months, even with the confounding effect of adjuvant therapy that was given in all patients. Overall QOL is improved after 3 months post IRE and does not have long term adverse QOL effects in majority of patients.

Introduction

- Pancreatic cancer is known to have a poor prognosis, one and five year survival rates of 28% and less than 5% respectively.[1,2] This form of cancer is the 4th most common cause of cancer related death in the United States.[2] Literature has identified multiple risk factors that cause pancreatic adenocarcinoma including smoking, obesity, diabetes, and chronic pancreatitis.
- Various surgical therapies have been studied including radiofrequency ablation, stereotactic body radiation therapy, high-intensity focused ultrasound, and irreversible electroporation (IRE) to treat pancreatic adenocarcinoma.[3]
- IRE is a non-thermal based ablation therapy that delivers a high electrical energy pulse to a defined tissue volume. The pulse alters the transmembrane potential across the cell membrane, disturbs the lipid bilayer, and causes permanent nanopore formation.[4] This will cause disruption in cellular homeostasis and initiate apoptosis.[5]
- This technology has been proven to be both safe and effective[6], but few studies have examined the beneficial aspects of IRE. Some literature has explored the quality of life for use of IRE in prostate cancer, but no literature has examined beneficial nature of IRE for locally advanced pancreatic cancer (LAPC).

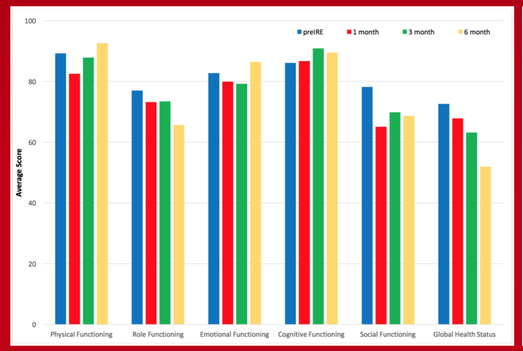
Hypothesis and Aims

- Patients diagnosed with LAPC and treated with IRE will report no detrimental effect to quality of life after treatment as defined by patient perceived symptom severity and functional status assessment.
- The aim of this study was to evaluate the quality of life via questionnaires provided before and after treatment of patients undergoing IRE and assess if a statistically significant beneficial difference was present among the questionnaire categories.

Results

Table 1: Baseline demographic and medical history

Patient Characteristics			
Median age (range)	59.08 (27.38-75.72)		
Gender		**Past medical History**	
Male (%)	19(45.2)	Cardiac	4
Female (%)	23(54.8)	Vascular	5
BMI (avg ± SD)	24.09 ± 3.78	Pulmonary	5
Race		Diabetes	8
white	39	Hypertension	12
African American	2	Smoking	16
other	1	Alcohol	5
Adjuvant Therapy	37		
Hospital Stay (avg ± SD)	12.71 ± 9.43		



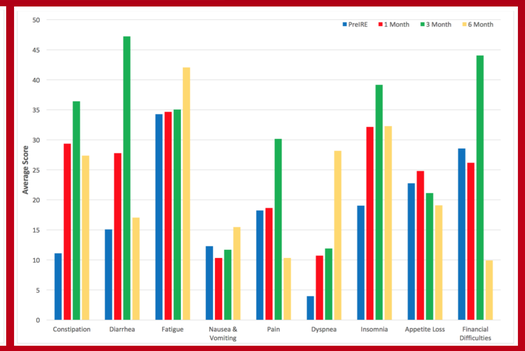


Table 2: One-way repeated measure ANOVA and Bonferoni post-hoc statistical analysis results for symptom severity, Functional assessment, global health status, and financial difficulties scales

ANOVA									
Scales	Time Points	Mean	ANOVA P-Value	Post-Test Significance (Bonferoni)					
				PreIRE-1	PreIRE-3	PreIRE-6	1-3	3-6	1-6
Physical Functioning	PreIRE	89.27	**0.004**	0.48	1.00	1.00	0.5	0.17	**0.003***
	1 month	82.52							
	3 month	87.82							
	6 month	92.62							
Role Functioning	PreIRE	76.98	0.31	1.00	1.00	0.36	1.00	1.00	1.00
	1 month	73.21							
	3 month	73.41							
	6 month	65.67							
Emotional Functioning	PreIRE	82.74	0.233	1.00	1.00	1.00	1.00	0.46	0.29
	1 month	79.93							
	3 month	79.23							
	6 month	86.44							
Cognitive Functioning	PreIRE	86.11	0.58	1.00	1.00	1.00	1.00	1.00	1.00
	1 month	86.71							
	3 month	90.87							
	6 month	89.48							
Social Functioning	PreIRE	78.18	0.05	0.10	0.44	0.46	1.00	1.00	1.00
	1 month	65.08							
	3 month	69.84							
	6 month	68.65							
Global Health Status	PreIRE	72.62	**0.001**	1.00	**0.02***	**0.001***	0.63	0.18	**0.05***
	1 month	67.86							
	3 month	63.19							
	6 month	51.99							
Constipation	PreIRE	11.11	**0.007**	0.07	**0.01***	0.01	1.00	1.00	1.00
	1 month	29.37							
	3 month	36.51							
	6 month	27.38							
Diarrhea	PreIRE	15.08	**<0.001**	**0.04***	**<0.001***	1.00	**0.001***	**<0.001***	0.20
	1 month	27.78							
	3 month	47.22							
	6 month	17.06							
Fatigue	PreIRE	34.26	0.49	1.00	1.00	0.753	1.00	1.00	1.00
	1 month	34.66							
	3 month	35.05							
	6 month	42.06							
Nausea & Vomiting	PreIRE	12.30	0.53	1.00	1.00	1.00	1.00	1.00	0.989
	1 month	10.32							
	3 month	11.71							
	6 month	15.48							
Pain	PreIRE	18.25	**0.002**	1.00	0.10	0.35	0.10	**0.001***	0.20
	1 month	18.65							
	3 month	30.16							
	6 month	10.32							
Dyspnea	PreIRE	3.97	**<0.001**	0.15	0.13	**<0.001***	1.00	**0.04***	**0.03***
	1 month	10.71							
	3 month	11.90							
	6 month	28.18							
Insomnia	PreIRE	19.05	**0.003**	0.13	**0.006***	0.14	1.00	1.00	1.00
	1 month	32.14							
	3 month	39.15							
	6 month	32.28							
Appetite Loss	PreIRE	22.76	0.64	1.00	1.00	1.00	1.00	1.00	1.00
	1 month	24.80							
	3 month	21.14							
	6 month	19.10							
Financial Difficulties	PreIRE	28.57	**<0.001**	1.00	0.15	**0.002***	**0.02***	**<0.001***	**0.05***
	1 month	26.19							
	3 month	44.05							
	6 month	9.92							

Table 3: Effect size calculation results for functional assessment, symptom severity, global health status, and financial difficulties scales. Large effect size (ES ≤ 0.8) bolded.

Effect size									
Scale	Time point	mean	SD	Common stdev	Difference between means			Effect Size		
					PreIRE-1	PreIRE-3	PreIRE-6	PreIRE-1	PreIRE-3	PreIRE-6
Physical Functioning	PreIRE	89.27	18.71	14.84	6.75	1.46	-3.35	0.45	0.1	0.23
	1 month	82.52	16.36							
	3 month	87.82	13.76							
	6 month	92.62	8.57							
Role Functioning	PreIRE	76.98	31.22	28.60	3.77	3.56	11.31	0.13	0.01	0.40
	1 month	73.21	25.67							
	3 month	73.41	29.17							
	6 month	65.67	28.05							
Emotional Functioning	PreIRE	82.74	15.99	16.93	2.81	3.50	-3.70	0.17	0.21	0.22
	1 month	79.93	18.47							
	3 month	79.23	20.91							
	6 month	86.44	10.63							
Cognitive Functioning	PreIRE	86.11	16.83	15.60	-0.60	-4.76	-3.37	0.04	0.31	0.22
	1 month	86.71	19.04							
	3 month	90.87	15.04							
	6 month	89.48	10.09							
Social Functioning	PreIRE	78.18	23.71	26.37	13.10	8.34	9.53	0.50	0.32	0.36
	1 month	65.08	31.79							
	3 month	69.84	24.96							
	6 month	68.65	24.19							
Global Health Status	PreIRE	72.62	20.85	21.57	4.76	9.43	20.63	0.22	0.44	**0.96***
	1 month	67.86	20.04							
	3 month	63.19	16.77							
	6 month	51.99	27.26							
Constipation	PreIRE	11.11	27.22	33.41	-18.25	-25.40	-16.27	0.55	0.76	0.49
	1 month	29.37	36.41							
	3 month	36.41	46.45							
	6 month	27.38	15.54							
Diarrhea	PreIRE	15.08	24.64	25.76	-12.70	-32.14	-1.99	0.49	**1.24***	0.08
	1 month	27.78	25.20							
	3 month	47.22	25.22							
	6 month	17.06	26.92							
Fatigue	PreIRE	34.26	26.08	26.45	-0.40	-0.80	-7.81	0.02	0.03	0.30
	1 month	34.66	26.11							
	3 month	35.05	22.14							
	6 month	42.06	30.75							
Nausea & Vomiting	PreIRE	12.30	27.56	20.34	1.99	0.60	-3.17	0.10	0.03	0.16
	1 month	10.32	19.37							
	3 month	11.71	16.57							
	6 month	15.48	15.68							
Pain	PreIRE	18.25	17.96	22.48	-0.40	-11.90	7.94	0.02	0.53	0.35
	1 month	18.65	22.53							
	3 month	30.16	27.54							
	6 month	10.32	20.81							
Dyspnea	PreIRE	3.97	10.92	20.53	-6.75	-7.94	-24.21	0.33	0.39	**1.18***
	1 month	10.71	16.80							
	3 month	11.90	18.87							
	6 month	28.18	30.47							
Insomnia	PreIRE	19.05	21.01	29.38	-13.10	-20.11	-13.23	0.45	0.68	0.45
	1 month	32.14	33.01							
	3 month	39.15	32.02							
	6 month	32.28	29.94							
Appetite Loss	PreIRE	22.76	32.01	26.25	-2.03	1.63	3.66	0.08	0.06	0.14
	1 month	24.80	30.53							
	3 month	21.14	22.06							
	6 month	19.10	17.70							
Financial Difficulties	PreIRE	28.57	26.10	30.43	2.38	-15.48	18.65	0.08	0.51	0.61
	1 month	26.19	31.70							
	3 month	44.05	40.29							
	6 month	9.92	19.84							

Methods

- Only patients with LAPC determined resectable or borderline resectable and receiving IRE were considered and offered a questionnaire.
- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 V2.0 (EORTC QLQ-C30 V2.0) were provided before surgery and 1,3 and 6 months after surgery. Questionnaire examined 15 categories including symptom severity, functional assessment, financial difficulty, and global health status.
- Scoring, analysis and interpretation followed guidelines published in the scoring manual[7].
- Descriptive statistics, one-way repeated measure ANOVA and effect size calculations were used to evaluate for significant differences among questionnaire categories. P-value ≤ 0.05 was considered significant.

Conclusions & Future Directions

- No significant differences were seen in functional assessment, but 62.5% of the symptoms scales showed worsening symptomatology with a preponderance of 3-6 months after treatment.
- Factors including statistically significant symptom profile, majority of patients undergoing adjuvant therapy, and timing of symptom onset suggest other interrelated clinical factors (e.g. chemotherapy toxicity) influenced results. Likely IRE therapy does not adversely affect quality of life.
- Future research involves utilizing other metrics for quality of life via different questionnaires to validate results. Additionally, comparing this data to other quality of life data for other common surgical therapies for LAPC will also highlight the beneficial affects of the treatment.

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Novel drug combinations sensitize leukemia cells to a Bcl-2 inhibitor

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Introduction

Leukemia is a diverse disease which will cause 24,400 deaths and 13.5 new cases per 100,000 individuals in 2016, according to the CDC. Current treatment options may lead to stable but chronic disease, but with few remissions that often relapse. Armed with this information, it is imperative that new treatment options are explored. An important method for leukemia cells to evade destruction is with alterations in the apoptotic pathway. Some of the most well known regulators of the apoptosis are the Bcl-2 family of proteins that are identified by the presence of motifs called BCL homology (BH) domains. Normally, Bcl-2 inhibits the activity of BAX and BAK, preventing cytochrome C release from the mitochondria. When a cell makes the decision to die, the amount of pro-apoptotic signals overwhelm the anti-apoptotic signals. Cell death can be induced through the intrinsic pathways where BH3 is activated and binds Bcl-2 allowing the permealization of mitochondria, caspase cleavage, and cell death. This makes the anti-apoptotic B-cell Lymphoma 2 (Bcl-2) proteins an interesting target for therapy. ABT737, and it oral analog ABT263, have been shown to act as BH_3 mimetics, binding Bcl-2, Bcl-X_L, and Bcl-w to promote apoptosis. Studies have shown that 30-50% protection of cancer cells to chemotherapeutic agents is from Bcl2 and Bcl-XL. Previous in silico drug screening was performed and synergy scores were assigned to varying drugs or compounds in combination with ABT737, with negative 100 representing total cell death. Compounds were chosen based on their synergy with ABT and exploration of the literature. This study aims to investigate the synergy or addidtive effects of Amiodarone or Amitriptyline with ABT compounds

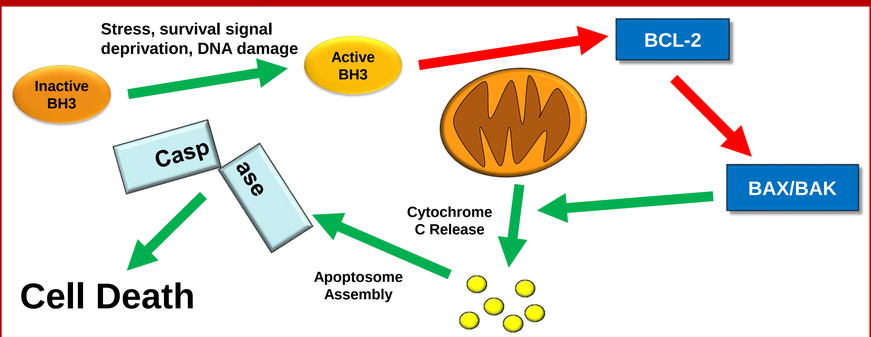
Compounds of Interest

Drug	Action	Average Synergy Score
Amiodarone hydrochloride	Class III antiarrhythmic, potassium channel blocker	-41.85
Amitriptyline hydrochloride	Tricyclic antidepressant, inhibits the norepinephrine and serotonin transporters	-51.78

Hypothesis

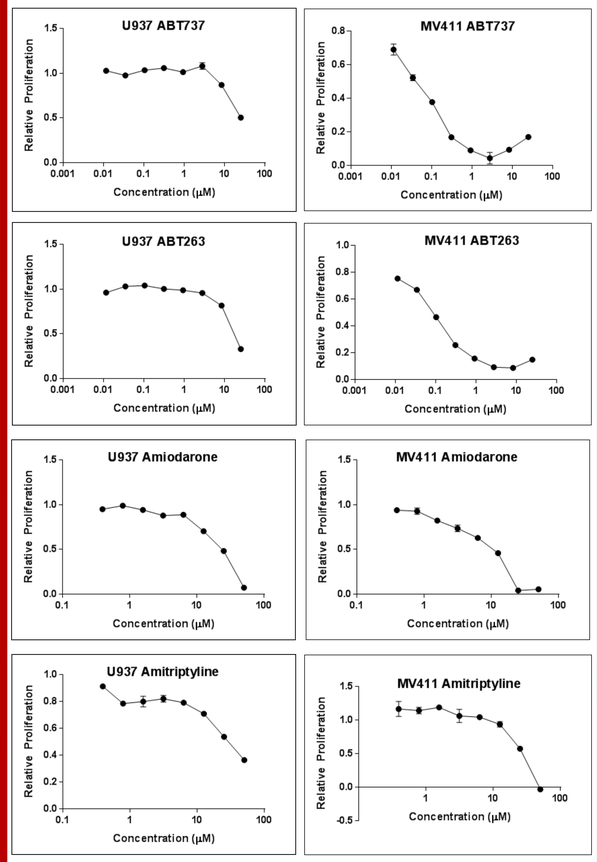
ABT263/737, in combination with Amiodarone or Amitriptyline, will decrease leukemia cell survival.

Intrinsic Apoptosis Cascade

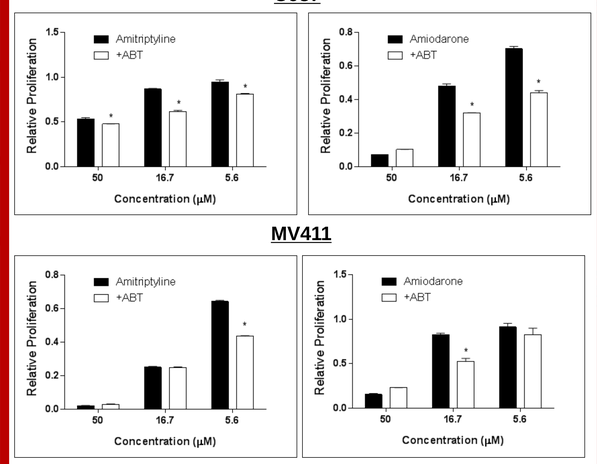


Results

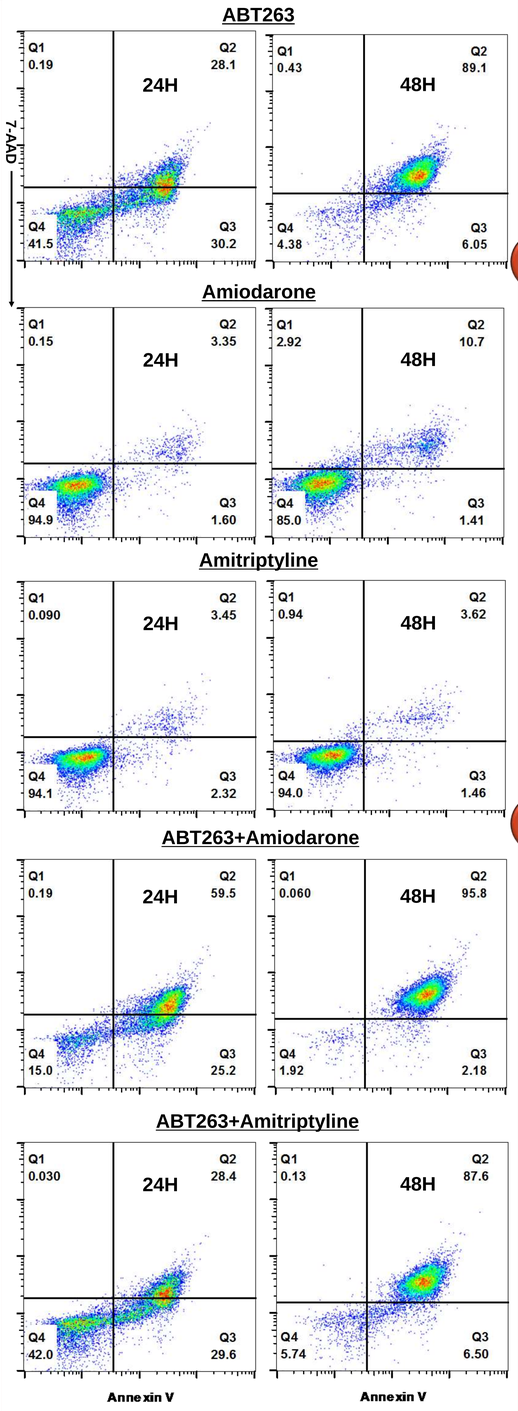
1 Drug Dose Response Curves



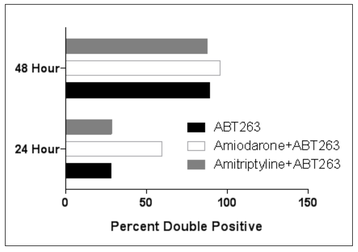
2 Drug Dose Response Curves



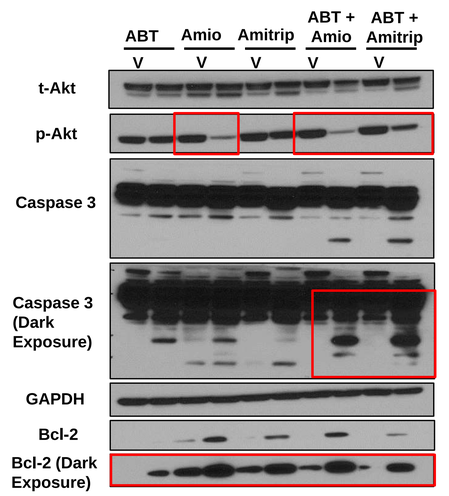
3 Flow Cytometry U937 – 24 & 48 Hours



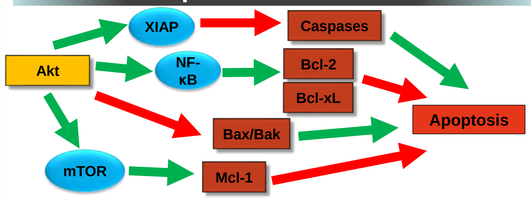
4 Quantified Flow Cytometry



5 Immunoblot – 6 Hour Drug Treatment



6 Proposed Mechanism



Conclusions

- ABT263/737, Amiodarone, and Amitriptyline decrease proliferation in leukemia cells
- In combination the IC_{30} of ABT737, Amiodarone and Amitriptyline decrease proliferation compared to the drug alone
- When the IC_{30} of Amiodarone is combined with the IC_{30} of ABT263, there is an increase in apoptosis at 24 and 48 hours
- U937 cells treated with Amiodarone +/- ABT or Amitriptyline +ABT have decreased p-Akt at 6 hours
- Amitriptyline and Amiodarone have increased caspase 3 cleavage when combined with IC_{30} of ABT263 at 6 hours

Acknowledgements

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Comprehensive Geriatric Assessment for Hepatopancreatobiliary Surgical Patients – A Systematic Review

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Introduction

- Cancer incidences for both liver and pancreatic neoplasms are expected to increase from 2010 to 2030 by 59% and 55%, respectively.
- As a result, more oncogeriatric patients will be presenting for curative surgeries in the future.
- The Comprehensive Geriatric Assessment (CGA) is a multidimensional diagnostic tool used by healthcare providers to assess the overall health status of elderly patients and identify patients at risk of postoperative complications.
- For hepatopancreatobiliary (HPB) patients with impaired health status as identified by preoperative CGA screening, it is necessary to address correctable deficits to ensure favorable outcomes.

Purpose of Study

- The aim of this review is to systematically assess the available literature with regards to CGA use for elderly patients undergoing HPB cancer surgeries, and identify the particular components that are best predictive of adverse postoperative outcomes.

Methods

- A literature search was conducted utilizing scholarly databases to identify primary research articles that included a geriatric assessment for patients undergoing HPB surgery.
- Searches were done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.
- Relevant studies were included if the following criteria were met: (i) Studies were either randomized clinical trials (RCT) or non-RCTs. (ii) Oncogeriatric participants were given all or part of a Comprehensive Geriatric Assessment (CGA). (iii) Patients underwent elective surgery for solid HPB tumors. (iv) Outcomes variables were explicitly reported.
- The quality of included studies was assessed using a modified Newcastle-Ottawa Scale.
- A critical systematic review was conducted on identified literature.

Results

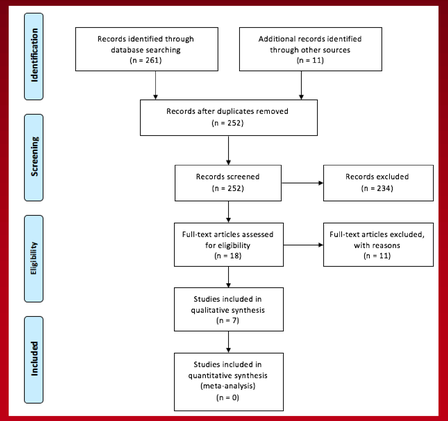

Figure 1. PRISMA Flow Diagram

Study	Functional Status	Performance Status	Mobility	Frailty Assessment	Mental Status	Mood/Depression	Nutritional Assessment	Polypharmacy	Social Support	Risk Assessment	Comorbidities	Laboratory Values
Badgwell et al. (2013)	X	X		X	X	X	X	X		X	X	
Dale et al. (2014)		X	X	X	X		X			X	X	
Huisman et al. (2014)			X				X			X	X	X
Huisman et al. (2015)	X	X	X	X	X	X	X			X	X	X
Kaibori et al. (2016)				X	X	X	X				X	X
Kenig et al. (2015)	X	X	X	X	X	X	X	X	X	X	X	X
Korc-Grodzicki et al. (2015)	X	X		X	X		X	X	X	X	X	X

Figure 2. Comprehensive Geriatric Assessment Components
- 12 categorical domains of the Comprehensive Geriatric Assessment were assessed in studies

Figure 3. Study Characteristics
- 7 articles were identified and used in the review assessment.
- The mean age of participants within studies varied from 67.3 to 80 years of age.
- The average study size was 191 patients.
- All studies included both male and female participants, with gender ratios varying widely between studies.

Study	Country	Quality Score	Study Design	Sample Size	Age (years)	Gender	Surgery Type	Outcome Measures
Badgwell et al. (2013)	United States	9	P	111	72 (65-89)	M 55.0% F 45.0%	Major abdominal (17% hepatic resection, 14% pancreatic resection)	i. 90-d any morbidity or mortality ii. 90-d major morbidity or mortality iii. Discharge to SNF iv. LOS v. 30-d readmission
Dale et al. (2014)	United States	9	P	76	67.3	M 55.3% F 44.7%	100% PD	i. morbidity or mortality ii. ICU admission iii. Discharge to SNF iv. LOS v. 30-d readmission
Huisman et al. (2014)	Multi-National	10	P	263	76 (73-81)	M 33.5% F 66.5%	Solid tumor removal (10.3% HPB)	i. 30-d morbidity or mortality ii. LOS iii. ICU admission iv. number of additional specialties involved in patient care
Huisman et al. (2015)	Multi-National	10	P	328	76 (70-96)	M 38.1% F 61.9%	Solid tumor removal (10.3% HPB)	i. 30-d major morbidity or mortality
Kaibori et al. (2016)	Japan	8	P	71	78 (70-89)	M 73.2% F 26.8%	100% liver resection for hepatocellular carcinoma	i. 1, 3, 6-mo morbidity
Kenig et al. (2015)	Poland	9	P	75	73 (65-93)	M 56.0% F 44.0%	Solid abdominal tumor removal (14.7% pancreas cancer, 3% gallbladder)	i. 30-d any morbidity or mortality ii. 30-d major morbidity or mortality
Korc-Grodzicki et al. (2015)	United States	8	R	416	80 (75-98)	M 45.9% F 54.1%	Solid tumor removal (20% HPB)	i. postoperative delirium ii. LOS iii. Discharge to SNF iv. 30-d urgent care center visit v. 30-d readmission vi. 30-d mortality vii. 6-mo mortality

Conclusions

- While several CGA variables were significantly associated with adverse postoperative outcomes, there is no clear consensus as to which assessment components provide the most utility to HPB surgical patients.
- Although the CGA provides useful diagnostic clinical information, more study into HPB specific populations is warranted.

Results

- A total of 1,340 patients were included in the 7 articles.
- Only 2 studies were comprised solely of HPB surgical patients, with only a small percentage of the remaining studies' populations (range 10.3-21%) comprised of HPB surgical patients.
- Included studies were generally of high quality, with a median quality score of 9 (range 8-10).
- The aim of all studies included some variant of recording or analyzing baseline geriatric assessment variables in patients undergoing cancer surgery to identify risk factors that may be associated with adverse outcomes.
- Screening tests as part of the CGA varied markedly between studies, as did the outcome measures.
- Abnormal times on the Timed-Get-Up-And-Go (TUG) test were found predictive of postoperative complications in Huisman et al. (2014), Huisman et al. (2015), and Kenig et al. (2015).
- The TUG test was predictive of increased length of hospital stays (>7 days) in Huisman et al. (2014).
- Dale et al. (2014) found that self-reported exhaustion, one of the five components of Fried's frailty criteria, was positively associated with predicting major complications in patients undergoing pancreatoduodenectomy.
- Patients who presented preoperatively with impaired nutritional status, measured by the Nutritional Risk Screening-2002 (NRS-2002) or Geriatric 8 (G8) assessment tests, were associated with increased postoperative complications.

Acknowledgements

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Estimated Percentage Of Breast Volume Excision And Its Relationship With Quality Of Life And Satisfaction After Breast Conservation Therapy For Breast Cancer

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Introduction

- Breast Conservation Therapy (BCT, lumpectomy followed by radiation therapy) is the preferred method of treatment for early stage breast cancer.
- Cosmesis after BCT has been shown to have a significant effect on patient psychological well-being and emotional distress.
- It has been suggested that when the Estimated Percentage of Breast Volume Excised (EPBVE) during BCT exceeds 10%, patient satisfaction decreases.
- BREAST-Q is a patient-reported outcome module based on health focused quality of life (QofL) reports encompassing 9 domains.

Objective

- The objective of this study was to determine the effect on QofL exerted by EPBVE for those undergoing BCT. We hypothesized that those with an EPBVE ≥10% would report lower satisfaction.

Methods

Population

- Patients from a prospectively maintained breast cancer database treated with BCT, stages 0-III, and with at minimum 1 year follow up, were evaluated after Institutional Review Board approval.
- Exclusion Criteria: incomplete records, bilateral disease, recurrence, death.

Mailing

- Subjects were mailed the BREAST-Q survey, introduction letter, and return envelope.
- If no response was received, after 2 weeks, a second mailing and a follow up phone call ensued.

BREAST-Q

- Patients reported satisfaction and QofL in 9 domains: breast, sexual, radiation, psychological, physical, information, surgeon, medical team, and non-medical staff.

Methods Continued

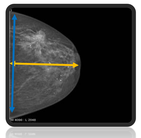
EPBVE

- Excised Breast Volume (EBV) was estimated from surgical pathology reports. If additional margins were applicable, they were added to the EBV.

$$EBV = \frac{4}{3}\pi\, r_1 \times r_2 \times r_3$$

Breast Volume (BV) was calculated using a previously validated formula from mammographic CC view.

$$BV = \frac{1}{3}\pi \left(\frac{Base}{2}\right)^2 \times height$$



- EPBVE was calculated.

$$EPBVE = \left(\frac{EBV}{BV}\right) \times 100$$

- Patients were grouped based on EPBVE $< 10\%$ or $\geq 10\%$

Statistics

- Univariate analysis was performed utilizing two sample T-test and chi square tests.
- ANOVA was used to determine the effect of each parameter for satisfaction with breasts.

Table 1 Univariate Analysis

		EPBVE <10	EPBVE ≥10%.	p Value
Age	30-60 years	28 (54%)	14 (45%)	**0.44**
	61-90 years	24 (46%)	17 (55%)	
Location	Lateral	28 (56%)	19 (65%)	**0.41**
	Medial	22 (44%)	10 (35%)	
Side	Left	25 (48%)	17 (55%)	**0.55**
	Right	27 (52%)	14 (45%)	
Stages	0	13 (25%)	7 (23%)	**0.97**
	I	26 (50%)	15 (48%)	
	II	12 (23%)	8 (26%)	
	III	1 (2%)	1 (3%)	
ER	Positive	40 (77%)	28 (96%)	**0.13**
	Negative	12 (23%)	3 (4%)	
HER2	Positive	5 (12%)	1 (17%)	**0.41**
	Negative	36 (88%)	22 (38%)	
SLNB	Yes	34 65%)	22 (71%)	**0.60**
	No	18 (35%)	9 (29%)	
ALND	Yes	5 (6%)	2 (10%)	**0.62**
	No	47 (94%)	29 (90%)	
Chemotherapy	Yes	7 (17%)	4 (14%)	**0.94**
	No	38 (71%)	17 (75%)	
	NAC	6 (12%)	3 (11%)	
Radiation Therapy	Yes	40 (80%)	25 (100%)	**0.03**
	No	10 (20%)	0	
Hormonal Therapy	Yes	31 (72%	22 (88%)	**0.13**
	No	12 (28%)	3 (12%)	
Margin re-excision	Yes	1 (2%)	11 (35%)	**<0.01**
	No	51 (98%)	20 (65%)	

Table 2 BREAST-Q Score Analysis

Parameters	EPBVE <10% Mean scores (± Std. dev)	EPBVE ≥10%. Mean scores (± Std. dev)	p Value
Breast Satisfaction	72.30 (20.90)	66.48 (20.85)	**0.22**
Sexual Satisfaction	63.84 (19.46)	58.90 (15.79)	**0.32**
Satisfaction with Radiation	85.76 (16.49)	89.52 (12.70)	**0.29**
Psychological Satisfaction	80.10 (19.10)	78.87 (20.75)	**0.79**
Physical Satisfaction	74.65 (22.64)	75.94 (18.53)	**0.79**
Satisfaction with Information	86.72 (18.06)	82.40 (18.51)	**0.31**
Satisfaction with Surgeon	94.90 (12.37)	89.93 (20.00)	**0.22**
Satisfaction with Staff	95.26 (13.05)	95.93 (13.50)	**0.83**
Satisfaction with Medical Team	94.45 (8.58)	97.70 (12.60)	**0.92**

Table 3 ANOVA for Breast Satisfaction

		Mean scores (± Std. dev)	Ranges	p Value
Location	Lateral (n = 38)	68.86 (19.84)	27-100	**0.63**
	Medial (n = 27)	71.85 (22.34)	33-100	
Side	Left (n = 31)	70.93 (19.82)	27-100	**0.47**
	Right (n = 34)	69.35 (21.92)	27-100	
Stages	0 (n = 15)	63.27 (22.65)	27-100	**0.35**
	I (n = 28)	70.96 (19.41)	33-100	
	II (n = 20)	74.40 (21.88)	37-100	
	III (n = 2)	66.5 (10.60)	59-74	
Chemotherapy	Yes (n = 11)	70.55 (21.91)	37-100	**0.17**
	No (n = 45)	67.93 (20.89)	27-100	
	NAC (n = 9)	80.44 (17.68)	52-100	
Radiation	Yes (n = 60)	70.03 (21.34)	27-100	**0.55**
	No (n = 5)	71.00 (14.07)	55-91	
Hormonal	Yes (n = 51)	70.01 (19.81)	33-100	**0.89**
	No (n = 14)	70.43 (24.88)	27-100	
Margin re-excision	Yes (n = 9)	73.88 (18.62)	52-100	**0.78**
	No (n = 56)	69.50 (21.21)	27-100	
EPBVE	<10 (n= 40)	72.30 (19.92)	27-100	**0.14**
	≥10 (n= 25)	66.60 (22.07)	27-100	

Terms in Tables: HER2, Human Epidermal Growth Factor Receptor 2; ER, Estrogen Receptor; SLNB, Sentinel Lymph Node Biopsy; ALND, Axillary Lymph Node Dissection; NAC, Neoadjuvant Chemotherapy

Results

- Of 290 patients, 77 met exclusion criteria.
- 213 patients were mailed the BREAST-Q survey. 83 (38.9%) responses were obtained. Responses per domain varied from 100% for overall satisfaction to 37% for sexual satisfaction.
- Univariate analysis (EPBVE of ≥10%, n=52 vs. <10%, n=32) showed that age, tumor location in breast, side, stage, ER status, HER2 status, sentinel or axillary lymph node dissection, chemotherapy, or hormonal therapy use are independent of EPBVE groups. (Table 1)
- The ≥10% group had greater percentage of adjuvant radiation therapy use (p=0.03) and margin re-excision (p<0.01). (Table 1)
- Univariate analysis demonstrated no significant differences amongst EPBVE groups mean scores in all 9 modules. (Table 2)
- ANOVA did not show that any parameter, including, EPBVE, significantly influenced overall satisfaction (p>0.05 for all). (Table 3)

Conclusions

•EPBVE <10 vs. ≥10 does not appear to impact satisfaction or QofL after BCT.
•The relationship between EPBVE, QofL, and satisfaction after BCT needs further analysis to determine the level at which this parameter becomes significant.
•Survey based analysis of satisfaction and QofL after BCT are limited by low response rates.

Acknowledgement

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KCC Expression and Function May Contribute to Human Cancer Cell Motility

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ABSTRACT

Introduction: Changes in cell shape and volume mediated by ion and water flux across cell membranes is an important part of cell migration. Previous studies have demonstrated the importance of K-Cl cotransporters (KCCs) in a chemically-induced rat glioblastoma cell line (C6). Inhibition of KCC3 using siRNA reduced C6 cell migration by ~50% in an *in vitro* scratch wound assay. De-phosphorylation of specific threonine residues within the intracellular cytoplasmic tail of the KCCs by protein phosphatase 1A (PP1A) results in cotransporter activation.

Objective: The present study aimed to further characterize the expression and regulation of the KCC family of proteins in the motility of a human melanoma (B16F10) and a human breast cancer (MDA 231) cell line.

Methods: B16F10 and MDA231 cells were both grown to confluence in 10 cm diameter cell culture dishes with Dulbecco's minimum essential media including 10% fetal bovine serum and 1% penicillin/streptomycin in a humidified 37°C incubator with 95% O_2/5% CO_2. Crude membrane preparations were subjected to SDS-PAGE and immunoblotted for KCC1, KCC3, KCC4, and PP1A proteins. B16F10 and MDA231 cells were also grown to 50% confluence on coverslip glass and immunofluorescently imaged by confocal microscopy for KCC1, KCC3, and KCC4 proteins with and without Calyculin A (PP1A inhibitor) treatment.

Results: For both cell lines, western blotting showed KCC1 and KCC4 enriched in crude membrane protein isolates. PP1A was also expressed in both crude membrane and soluble protein isolates. Immunofluorescent localization of KCC1, KCC3, and KCC4 expression was intracellularly diffuse with the strongest signal peri-nuclear. Treatment with Calyculin A (5 nM) for 1 h resulted in a morphological change in cell phenotype from flattened with many filopodia to rounded and swollen appearance without visible filopodia. This morphological change was reversible when the Calyculin A was removed and the cells were cultured in control media for 10 h.

Conclusions: These results suggest that human cancer cell lines express KCC1, 3, and 4 proteins as well as an important regulator of their activity, PP1A. The KCC subtypes show somewhat different distributions with KCC1 and KCC4 exhibiting strong plasma membrane expression by western blotting, while all three isoforms showed intracellular expression by immunofluorescent microscopy. Based on the Calyculin A studies, we conclude that PP1A activity is critical for filipodia development and directional cell motility. The role of individual KCC isoforms in these cancer cell structural changes remain to be determined.

INTRODUCTION

Changes in cell shape and volume mediated by ion and water flux across cell membranes is an important part of cell migration. The K-Cl cotransporter (KCC) family of proteins are capable of regulating ion flux across cell membranes by symport of potassium and chloride ions in a 1-to-1 ratio. KCCs are 130-150 kDa proteins capable of forming both homo- and hetero-dimers. KCC activity is shut off by kinase-mediated phosphorylation (e.g. SPAK, Ste20-like proline-alanine rich serine/threonine kinase), whereas activity of KCCs is stimulated by protein phosphatase 1A (PP1A). The capacity of migrating cells to adjust their cell volume (i.e. KCC activity) and shape may aid in invasion into tissues. Therefore, it is logical that interfering with the molecular mechanisms that are implicated in KCC regulation could be effective in reducing growth and migration of cancer. Previous studies have shown that siRNA-mediated knockdown of KCC3 reduced *in vitro* migration of chemically-induced rat glioblastoma cells. Another study found that a dominant negative mutant KCC1 reduced migration and growth when expressed in a human cervical cancer cell line.

The current project was designed to determine the presence of KCC1, KCC3, and KCC4 proteins in a human breast cancer cell line (MDA231) and a human melanoma cell line (B16F10), and observe the effect of KCC inhibition using Calyculin A (an inhibitor of PP1A) on cell volume and shape regulation.

METHODS

Cell Culture of Human skin (B16F10) and breast (MDA231) cancer cells.

B16F10 and MDA231 cells were cultured @37°C in a humidified incubator with 5% CO_2 in Minimal Essential Medium (MEM) with 10% Fetal bovine serum and 2% Penicillin/Streptomycin. Cells were split once per week at 1:10 ratio.

Western Blot Analysis

Total lysate samples were separated by SDS-Page, transferred to a nitrocellulose membrane, and immunoblotted with goat anti-KCC1 (1:100), rabbit anti-KCC3(1:100), rabbit anti-KCC4(1:100), and mouse anti-PP1A (1:500) antibodies overnight @ 4°C. Membranes were washed in T-TBS and incubated in species appropriate HRP-conjugated antibodies (1:5000) and anti-β actin HRP (1:10,000) for 1 h @ room temperature. Bands were visualized with enhanced chemiluminescence.

Confocal Microscopy

Cells cultured in 8-well chambered coverslip slides were washed with 1x PBS, treated with 5nM Calyculin A for 1 hour and/or and allowed to recover for 24 h before being fixed with 3.7% paraformaldehyde, permeabilized with 0.1% saponin, and incubated in goat anti-KCC1 (1:100), rabbit anti-KCC3(1:100), or rabbit anti-KCC4(1:100) antibodies overnight @ 4°C. Cells were washed with 1x PBS and incubated in species appropriate fluorescently-conjugated (488nm) antibodies (1:500) and 300nM DAPI for 1 h at room temperature. All cells were imaged using an Olympus Fluoview FV 100 confocal microscope, equipped with a 60x oil-immersion objective. All images were processed using the Olympus Fluoview Version 4.2 viewer program.

RESULTS

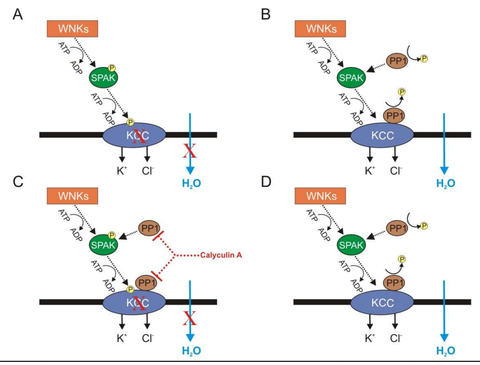

Figure 1. Model for inhibition and recovery of KCC activity following Calyculin A treatment. (A) KCC proteins are inactivated by kinase phosphorylation. (B) PP1 removes phosphate from KCC, thus permitting osmotic regulation of cell volume by KCC activity. (C) Calyculin A indirectly inhibits KCC activity by preventing dephosphorylation. (D) Removal of Calyculin A restores PP1A function and KCC activity.

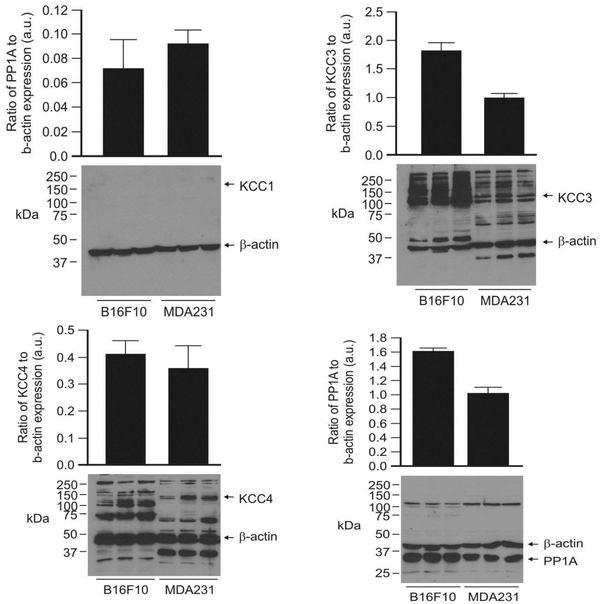

Figure 2. Relative expression of KCC and PP1A proteins in melanoma and breast cancer whole cell lysates. KCC1, KCC3, KCC4 and PP1A antibodies show signals in the expected kDa range for each protein. Bars represent densitometry measurements of 3 independent lysate samples. All experiments were repeated 3-5 times.

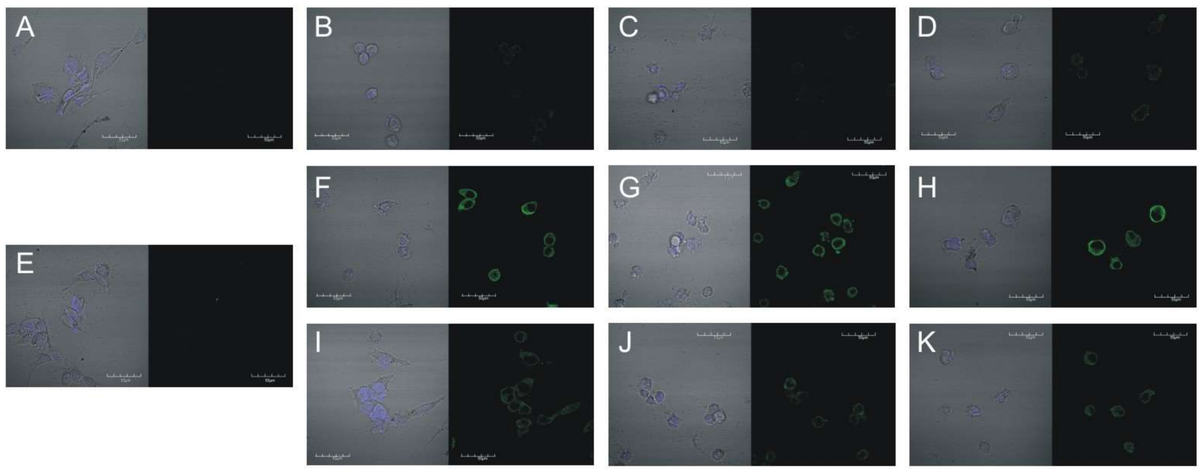

Figure 3. B16F10 cells shrink in response to Calyculin A treatment and recover following removal of Calyculin A. Secondary control (A,E). KCC1 (B,C,D). KCC3 (F,G,H). KCC4 (I, J, K). Unstimulated cells have numerus extensions of the plasma membrane (B, F, I). Calyculin A treatment for 1 hour leads to retraction of processes and a more rounded shape (C, G, J). After 24 hours of recovery in the absence of Calyculin A cells re-extend processes and resemble unstimulated cells(D, H, K). The relative signal strength of each KCC is consistent with the signal strength observed in western blots (Figure 1).

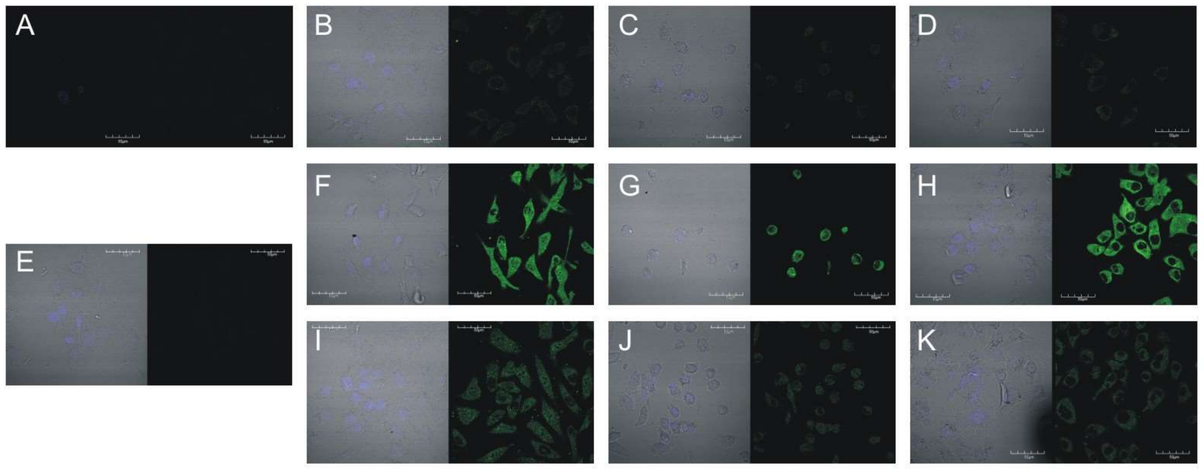

Figure 4. MDA321 cells shrink in response to Calyculin A treatment and recover following removal of Calyculin A. Secondary control (A,E). KCC1 (B,C,D). KCC3 (F,G,H). KCC4 (I, J, K). Unstimulated cells have numerus extensions of the plasma membrane (B, F, I). Calyculin A treatment for 1 hour leads to retraction of processes and a more rounded shape (C, G, J). After 24 hours of recovery in the absence of Calyculin A cells re-extend processes and resemble unstimulated cells(D, H, K). The relative signal strength of each KCC is consistent with the signal strength observed in western blots (Figure 1).

CONCLUSIONS

- Western blotting identified protein bands for KCC1, KCC3, KCC4, and PP1A within the expected size range for each respective protein.
- B16F10 and MDA231 cells express more KCC3 and KCC4 than KCC1.
- Immunofluorescence of KCC3 and KCC4 show a diffuse staining without a strong localization to the cell membrane.
- Calyculin A treatment lead to notable contraction of cellular processes and a more spherical shape.
- Interestingly, the effect of Calyculin A was reversible suggesting that volume regulation via KCC activity is important to cell migration.

ACKNOWLEDGMENTS

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A Prospective Study of Nasociliary Function and Rhinosinusitis Symptomatology in Patients with Oropharyngeal Squamous Cell Carcinoma Receiving Intensity Modulated External Beam Radiotherapy

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Abstract

Rhinosinusitis is any inflammation within the mucosal membranes of the paranasal sinuses and contiguous nasal lining. Changes in the nasal cavity such as mucosal dryness, crusting and other rhinosinusitis symptoms have been seen after external beam radiation. The impact of low dose radiation from intensity modulated radiation therapy (IMRT) on the nasal cavity and paranasal sinuses has not been fully described. We propose examining the dose-response relationship for mucociliary clearance time (MCT), nasal symptoms, and imaging findings of rhinosinusitis for low dosage of scatter radiation from IMRT to the oropharynx in order to establish better guidelines for organ tolerance and planning.

Methods

Methods/Materials: Forty patients with locally advanced squamous cell carcinoma of the oropharynx will be enrolled in an institutional review board (IRB) approved prospective study. MCT will be recorded via saccharin test at time of initial visit or CT simulation appointment and then again at 6 weeks following IMRT and 4 months following IMRT. Linear regression will be used to compare MCT before and after IMRT. The effects of rhinosinusitis on quality of life before and after radiation will be assessed via SNOT-22 questionnaire at the same time points as MCT. Radiographic changes to the sinonasal complex after radiation will be evaluated with an established staging system, the Lund-MacKay staging system. Lund-MacKay scores will be calculated at time of diagnostic CT and post-treatment CT. The above measures will then be analyzed through descriptive statistics and paired t-tests to determine which patients are most at risk for rhinosinusitis symptoms after IMRT. To study the effect of the various dose factors on the changes in MCT, linear regression will be implemented.

Results

Five patients were examined at their first follow up visit after completion of radiotherapy for definitive treatment of oropharynx malignancies to determine the ability to detect saccharine in the setting of oropharyngeal mucositis and dysgeusia. All patients were able to taste saccharine. It is expected that MCT before IMRT will be lower than MCT after IMRT. MCT is expected to increase at the 6-week measurement and then decrease during the 4-month measurement. It is expected that higher radiation doses to the sinonasal complex will have higher MCT values post treatment than lower dose treatment. Quality of life measures are expected to be higher before radiation treatment and should be relatively higher ffor patients receiving lower doses to the sinonasal complex compared higher doses. Lund MacKay scores are expected to worsen as dose factors are increased and after treatment.

Pt. #	Can Taste Saccharin	Cannot Taste Saccharin
1	x	
2	x	
3	x	
4	x	
5	x	
6	x	

Table 1: Saccharin Taste Test

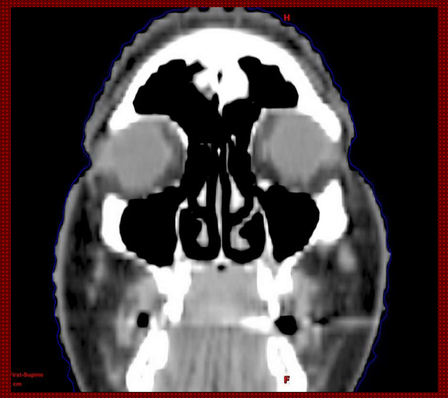

Figure 1: Initial Patient CT scan

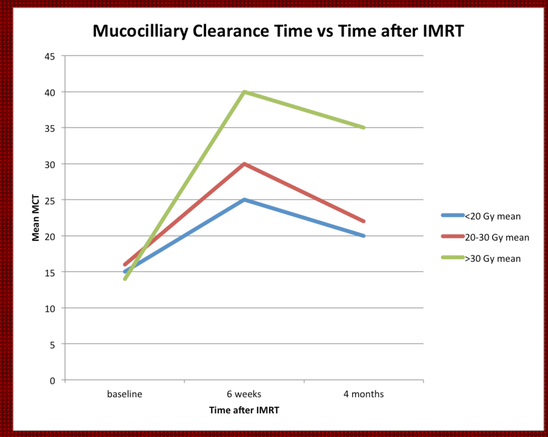

Figure 1: Expected MCT vs Time plotted at different dosages.

	No abnormality	Partial opacification	Total opacification
Anterior ethmoid			
R	0	1	2
L	0	1	2
Posterior ethmoid			
R	0	1	2
L	0	1	2
Maxillary			
R	0	1	2
L	0	1	2
Frontal			
R	0	1	2
L	0	1	2
Sphenoid			
R	0	1	2
L	0	1	2
Ostiomeatal complex	Non-obstructed		Obstructed
R	0		2
L	0		2

Table 2: Lund-Mackay Staging

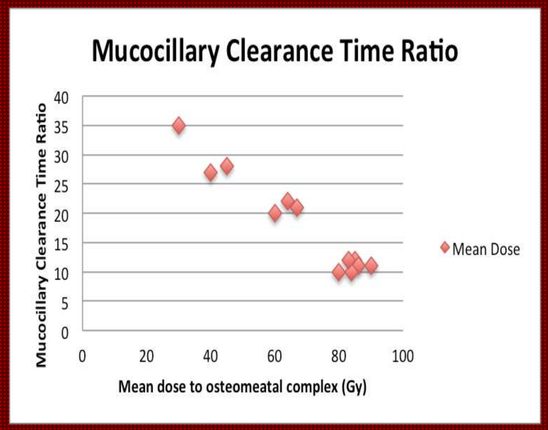

Figure 2: Expected MCT vs Dose to Osteomeatal Complex

Conclusions

Low dose radiation to the sinonasal complex negatively impacts the development of rhinosinusitis during radiation therapy to the oropharynx. The sinonasal complex should be included as an organ of risk during radiation treatment planning. Preventative strategies should be further explored in a randomized fashion.

Acknowledgements

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