Cancer Research 2019

Cancer Services, Hamad Medical Corporation

مؤسسة حمد الطبية
Hamad Medical Corporation
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Cancer Research 2019

Table of Contents

Introduction	3
Summary	4
Original Research Articles	6
Case Reports	67
Reviews	103
Abstracts	125
Conference Papers	151
Active Research Projects	163
Educational and Training Activities	168
Conferences and Workshops 2019	175
Index of Researchers	176

Introduction

Dear Colleagues,

Hamad Medical Corporation (HMC) is committed to developing excellence in comprehensive cancer services through the integration of clinical care, research and education at all levels as outlined in the National Cancer Framework 2017-2022.

Cancer research at HMC aims to provide innovation that will lead to improved care for cancer patients and reduces the risk of people developing cancer. Together with our academic partners we are continuously striving to advance the cancer research capability in Qatar.

We are proud to release the Cancer Research booklet for the year 2019. This booklet collates the research effort of our clinicians, nurses, pharmacists, research scientists and all allied health professionals and research staff. The booklet covers all the original researches, case reports, reviews, abstracts, conference papers that were published in 2019. The high quality of research conducted and published in 2019 demonstrates our commitment to advancing cancer research at HMC.

Dr. Mohammed Ussama Al Homsi

Deputy Medical Director and Clinical Research and Education
National Center for Cancer Care and Research
Hamad Medical Corporation

Summary

Table 1- Research Publications in 2016, 2017, 2018,2019

Publications	2016	2017	2018	2019
Original Research Articles	26(51%)	33(24%)	21(15%)	32(21%)
Case Reports/Series	8(10%)	15(10%)	16(11%)	28(19%)
Review/Book Chapters	5(6%)	13(12%)	13(9%)	16(11%)
Abstracts	-	-	-	13(9%)
Conference Presentations	40(33%)	63(54%)	92(64%)	60(40%)
Dissertations and Thesis Papers	-	-	1(1%)	-
Total	79	124	143	149

Research Projects

There were 39 active research projects in 2019.

Research Output: Publications

A total of 149 research communications have been published or presented in national, regional, international journals or conferences during 2019. Of these 32 original research articles, 28 case reports/series, 16 review articles, 13 Abstracts and 60 conference presentations.

Publications

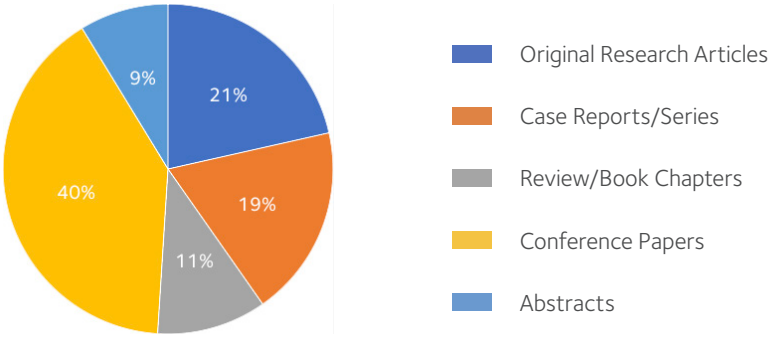

Figure 1 Publications in 2019 in different categories

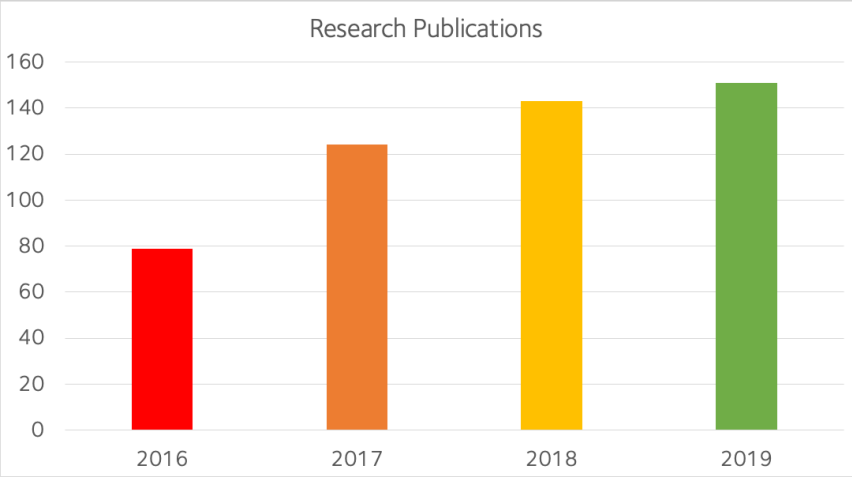

Figure 2 Research publications in 2016, 2017, 2018, 2019

Table 2 -Research Output Impact Factors 2017				
Impact Factors	**Original Articles**	**Case Reports**	**Reviews**	**Total**
0-1	13	9	4	26
1-2	2	1	-	3
2-3	6	2	1	9
3-4	1	-	3	4
4-5	2	-	-	2
5-6	-	-	1	1
6-7	1	-	-	1
7-8	1	-	1	2
8-9	-	-	-	-
9-10	-	-	-	-
>10	-	-	-	-

Table 3- Research Output Impact Factors 2018				
Impact Factors	Original Articles	Case Reports	Reviews	Total
0-1	6	10	3	19
1-2	2	2	1	5
2-3	6	-	1	7
3-4	2	-	1	3
4-5	1	-	1	2
5-6	1	1	1	3
6-7	1	-	1	2
7-8	-	-	1	1
8-9	-	-	-	-
9-10	-	-	-	-
>10	2	-	1	3

Table 4- Research Output Impact Factors 2019					
Impact Factors	Original Articles	Case Reports	Reviews	Abstracts	Total
0-1	1	8	1	-	10
1-2	3	3	3	-	9
2-3	7	4	2	3	16
3-4	1	2	6	-	9
4-5	12	1	-	1	14
5-6	2	-	1	-	3
6-7	1	-	2	-	3
7-8	1	1	-	3	5
8-9	2	-	-	-	2
9-10	2	-	-	-	2
>10	2	-	1	6	9

Original Research

Molecular Roulette: Nucleophosmin Mutations in AML Are Orchestrated Through N-nucleotide Addition by TdT

Julian Borrow [1,2], Sara A Dyer [1,2], **Susanna Akiki** [1,3], Michael J Griffiths [1,2]

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Abstract

Nucleophosmin (NPM1) is the most commonly mutated gene in acute myeloid leukemia (AML). AML with mutated NPM1 is recognized as a separate entity in the World Health Organization 2016 classification and carries a relatively favorable prognosis. NPM1 mutations are predominantly 4-bp duplications or insertions in the terminal exon that arise through an unknown mechanism. Here we analyze 2430 NPM1 mutations from 2329 adult and 101 pediatric patients to address their origin. We show that NPM1 mutations display the hallmarks of replication slippage but lack suitable germline microhomology available for priming. Insertion mutations display G/C-rich N-nucleotide tracts, with a significant bias toward polypurine and polypyrimidine stacking ($P < .001$). These features suggest terminal deoxynucleotidyl transferase (TdT) primes replication slippage through N-nucleotide addition, with longer syntheses manifesting as N-regions. The recurrent type A, type D, and type B mutations require 1, 2, and 3 N-nucleotide extensions of T, CC, and CAT, respectively, with the last nucleotide used as occult microhomology. This TdT-mutator model successfully predicts the relative incidence of the 256 potential 4-bp insertion/duplication mutations at position c.863_864 over 4 orders of magnitude ($\rho = 0.484$, $P < .0001$). Children have a different NPM1 mutation spectrum to adults, including a shift away from type A mutations and toward longer N-regions, consistent with higher TdT activity in pediatric myeloid stem cells. These findings complement our FLT3-ITD data, suggesting illegitimate TdT activity contributes to around one-half of AMLs. AML may therefore reflect the price for adaptive immunity.

Citation:

Borrow J, Dyer SA, Akiki S, Griffiths MJ. Molecular roulette: nucleophosmin mutations in AML are orchestrated through N-nucleotide addition by TdT. *Blood.* 2019;134(25):2291-2303.

Impact Factor: 10.660

Terminal Deoxynucleotidyl Transferase Promotes Acute Myeloid Leukemia by Priming FLT3-ITD Replication Slippage

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Abstract

FLT3-internal tandem duplications (FLT3-ITDs) are prognostic driver mutations found in acute myeloid leukemia (AML). Although these short duplications occur in 25% of AML patients, little is known about the molecular mechanism underlying their formation. Understanding the origin of FLT3-ITDs would advance our understanding of the genesis of AML. We analyzed the sequence and molecular anatomy of 300 FLT3-ITDs to address this issue, including 114 ITDs with additional nucleotides of unknown origin located between the 2 copies of the repeat. We observed anatomy consistent with replication slippage but could only identify the germline microhomology (1-6 bp) anticipated to prime such slippage in one-third of FLT3-ITDs. We explain the paradox of the "missing" microhomology in the majority of FLT3-ITDs through occult microhomology: specifically, by priming through use of nontemplated nucleotides (N-nucleotides) added by terminal deoxynucleotidyl transferase (TdT). We suggest that TdT-mediated nucleotide addition in excess of that required for priming creates N-regions at the duplication junctions, explaining the additional nucleotides observed at this position. FLT3-ITD N-regions have a G/C content (66.9%), dinucleotide composition ($P < .001$), and length characteristics consistent with synthesis by TdT. AML types with high TdT show an increased incidence of FLT3-ITDs (M0; $P = .0017$). These results point to an unexpected role for the lymphoid enzyme TdT in priming FLT3-ITDs. Although the physiological role of TdT is to increase antigenic diversity through N-nucleotide addition during V(D)J recombination of IG/TCR genes, here we propose that illegitimate TdT activity makes a significant contribution to the genesis of AML.

Citation:

Borrow J, Dyer SA, Akiki S, Griffiths MJ. Terminal deoxynucleotidyl transferase promotes acute myeloid leukemia by priming FLT3-ITD replication slippage. *Blood.* 2019;134(25):2281-2290.

Impact Factor: 10.660

Vaccination with nanoparticles combined with micro-adjuvants protects against cancer

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Abstract

Background - Induction of strong T cell responses, in particular cytotoxic T cells, is a key for the generation of efficacious therapeutic cancer vaccines which yet, remains a major challenge for the vaccine developing world. Here we demonstrate that it is possible to harness the physiological properties of the lymphatic system to optimize the induction of a protective T cell response. Indeed, the lymphatic system sharply distinguishes between nanoscale and microscale particles. The former reaches the fenestrated lymphatic system via diffusion, while the latter either need to be transported by dendritic cells or form a local depot. Method - Our previously developed cucumber-mosaic virus-derived nanoparticles termed ($CuMV_{TT}$-VLPs) incorporating a universal Tetanus toxoid epitope TT830–843 were assessed for their draining kinetics using stereomicroscopic imaging. A nano-vaccine has been generated by coupling p33 epitope as a model antigen to $CuMV_{TT}$-VLPs using bio-orthogonal Cu-free click chemistry. The $CuMV_{TT}$-p33 nano-sized vaccine has been next formulated with the micron-sized microcrystalline tyrosine (MCT) adjuvant and the formed depot effect was studied using confocal microscopy and trafficking experiments. The immunogenicity of the nanoparticles combined with the micron-sized adjuvant was next assessed in an aggressive transplanted murine melanoma model. The obtained results were compared to other commonly used adjuvants such as B type CpGs and Alum. Result - Our results showed that $CuMV_{TT}$-VLPs can efficiently and rapidly drain into the lymphatic system due to their nano-size of ~ 30 nm. However, formulating the nanoparticles with the micron-sized

MCT adjuvant of ~ 5 µM resulted in a local depot for the nanoparticles and a longer exposure time for the immune system. The preclinical nano-vaccine $CuMV_{TT}$-p33 formulated with the micron-sized MCT adjuvant has enhanced the specific T cell response in the stringent B16F10p33 murine melanoma model. Furthermore, the micron-sized MCT adjuvant was as potent as B type CpGs and clearly superior to the commonly used Alum adjuvant when total $CD8^+$, specific p33 T cell response or tumour protection were assessed. Conclusion - The combination of nano- and micro-particles may optimally harness the physiological properties of the lymphatic system. Since the nanoparticles are well defined virus-like particles and the micron-sized adjuvant MCT has been used for decades in allergen-specific desensitization, this approach may readily be translated to the clinic.

Key words:

Cucumber-mosaic virus CuMV, Virus-like particle VLP, Microcrystalline tyrosine MCT, Nano-vaccine

Citation:

Mohsen MO, Heath MD, Cabral-Miranda G, Lipp C, Zeltins A, Sande M, Stein JV, Riether C, Roesti E, Zha L, Engeroff P, El-Turabi A, Kundig TM, Vogel M, Skinner MA, Speiser DE, Knuth A, Kramer MF, Bachmann MF. Vaccination with nanoparticles combined with micro-adjuvants protects against cancer, *Journal for Immunotherapy of Cancer* (2019) 7:114.

Impact Factor: 8.767

The Study of Druggable Targets in Nonsquamous Non-Small-Cell Lung Cancer in the Middle East and North Africa

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in collaboration with the Arab Collaborative Hematology Oncology Group (ACHOG) King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, KSA, [1] BLIDA [1] University, CHU BLIDA, Algeria, [2] King Faisal Specialist Hospital and Research Center, Riyadh, KSA, [3] The American University of Beirut, Lebanon, [4] Weill Cornell Medical College/**Hamad Medical Corporation, Qatar,** [5] Tawam Hospital, UAE, [6] Princess Noorah Oncology Center, King Abdulaziz Medical City, [7] King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Jeddah, KSA, [8] Anti-Cancer Center, Oran, Algeria, [9] Centre Hospitalo Universitaire Ben Badis de Constantine, Constantine, Algeria

Abstract

Background: Druggable molecular targets are very important in the management of non-smallcell lung cancer (NSCLC). The purpose of our study is to determine the pattern of testing and mutation prevalence in the Middle East and North Africa population. Patients and Methods: Data of consecutive patients with nonsquamous NSCLC were collected from 10 centers in five countries; Saudi Arabia, UAE, Qatar, Lebanon, and Algeria. Statistical analysis was performed to delineate the prevalence of druggable targets and other relevant information. Results: Five hundred and sixty-six patients were included in the study. Majority were males (78.1%) with a median age of 61 years (22–89), 50% were current or ex-smokers and 370 patients (65.4%) were Stage IV. The epidermal growth factor receptor (EGFR) testing was performed on 164 patients of all stages. EGFR mutation was detected in 30 out of 96 patients (31.3%) with metastatic disease and in 12 out of 68 patients (17.6%) with Stage I to III. Female sex (39.5% vs. 22% males, P = 0.032), Stage IV (31.2% vs. 17.6% in Stage I to III, P = 0.049), and positive immunohistochemical-TTF1 (31.4% vs. 8.7% negative, P = 0.026) were predictors of mutation on univariate analysis. The multivariate analysis showed that patients with stage IV have three times higher positivity than lower stages (odds ratio = 3.495, P = 0.036). Anaplastic lymphoma kinase fusion was present in seven out of 89 patients (7.8%) of all stages, and only three out of 52 patients (5.8%) with metastatic disease. The reasons for not performing the tests in all of the 370 patients with metastatic disease were: physicians do not know where and how to send the test (62.3%), lack of funding to perform the test (11.1%), insufficient tissue (10.1%), and other reasons (16.6%). Conclusions: Only a small fraction of patients with NSCLC are tested for druggable targets and the prevalence of EGFR mutation is prevalence higher than the Western population. Overcoming the

challenges of testing requires systematic plans to address education and resource allocation.

Keywords:

Druggable, druggable targets, lung cancer, non-small-cell lung cancer, nonsquamous non-small-cell lung cancer

Citation:

Jazieh AR, Bounedjar A, Al Dayel F, et al, in collaboration with the Arab Collaborative Hematology Oncology Group (ACHOG). The study of druggable targets in nonsquamous non-small-cell lung cancer in the Middle East and North Africa. *Journal of Immunotherapy and Precision Oncology*, 2019; 2:4-7

Impact Factor: 8.728

Florid biliary duct lesions in an AMA -positive patient in absence of cholestatic liver biochemistry

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Abstract

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease, diagnosed by the presence of anti-mitochondrial antibodies (AMA) or highly PBC-specific anti-nuclear antibodies, in the appropriate context of cholestatic liver biochemistry.

We present a case with histological features of destructive granulomatous lymphocytic cholangitis affecting interlobular and septal bile ducts suggestive of PBC, with strong positive AMA, Anti-M2 and anti-nuclear dot, but with persistently normal alkaline phosphatase (ALP). On the contrary to previous reports suggesting that those individuals in whom ALP remains persistently below 1.5 times ULN appear to have a benign course and a better prognosis, our patient progressed to liver cirrhosis.

Citation:

Sultan K., Petkar M. and Derbala M., Florid biliary duct lesions in an AMA -positive patient in absence of cholestatic liver biochemistry, *Journal of Autoimmunity*,2019, 04.004

Impact Factor: 7.320

Protein Expression Profiling Identifies Key Proteins and Pathways Involved in Growth Inhibitory Effects Exerted by Guggulsterone in Human Colorectal Cancer Cells

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Abstract

Colorectal cancer (CRC) is a leading killer cancer worldwide and one of the most common malignancies with increasing incidences of mortality. Guggulsterone (GS) is a plant sterol used for treatment of various ailments such as obesity, hyperlipidemia, diabetes, and arthritis. In the current study, anti-cancer effects of GS in human colorectal cancer cell line HCT 116 was tested, potential targets identified using mass spectrometry-based label-free shotgun proteomics approach and key pathways validated by proteome profiler antibody arrays. Comprehensive proteomic profiling identified 14 proteins as significantly dysregulated. Proteins involved in cell proliferation/migration, tumorigenesis, cell growth, metabolism, and DNA replication were downregulated while the protein with functional role in exocytosis/tumor suppression was found to be upregulated. Our study evidenced that GS treatment altered expression of Bcl-2 mediated the mitochondrial release of cytochrome c which triggered the formation of apoptosome as well as activation of caspase-3/7 leading to death of HCT 116 cells via intrinsic apoptosis pathway. GS treatment also induced expression of p53 protein while p21 expression was unaltered with no cell cycle arrest. In addition, GS was found to inhibit NF-kB signaling in colon cancer cells by quelling the expression of its regulated gene products Bcl-2, cIAP-1, and survivin.

Keywords:

colorectal cancer, HCT 116, SW620, guggulsterone, label-free shotgun proteomics, intrinsic apoptosis pathway, NF-kB signaling

Citation:

Leo R, Therachiyil L, Siveen SK, Uddin S, Kulinski M, Buddenkotte J, Steinhoff M, Krishnankutty AR. Protein Expression Profiling Identifies Key Proteins and Pathways Involved in Growth Inhibitory Effects Exerted by Guggulsterone in Human Colorectal Cancer Cells. *Cancers (Basel).* 2019, 1;11(10):1478.

Impact factor: 6.162

Targeting Mutated Plus Germline Epitopes Confers Pre-Clinical Efficacy of an Instantly Formulated Cancer Nano-Vaccine

Mona O. Mohsen,[1,2,3,] Monique Vogel,[2] Carsten Riether,[4] Julius Muller,[1] Silvia Salatino,[5] Nicola Ternette,[1] Ariane C. Gomes,[1] Gustavo Cabral-Miranda,[2] Aadil El-Turabi,[1] Christiane Ruedl,[6] Thomas M. Kundig,[7] **Said Dermime**,[3] **Alexander Knuth**,[3] Daniel E. Speiser,[8] and Martin F. Bachmann[1,2]

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Abstract

Personalized cancer vaccines hold promises for future cancer therapy. Targeting neoantigens is perceived as more beneficial compared to germline, non-mutated antigens. However, it is a practical challenge to identify and vaccinate patients with neoantigens. Here we asked whether two neoantigens are sufficient, and whether the addition of germline antigens would enhance the therapeutic efficacy. We developed and used a personalized cancer nano-vaccine platform based on virus-like particles loaded with toll-like receptor ligands. We generated three sets of multi-target vaccines (MTV) to immunize against the aggressive B16F10 murine melanoma: one set based on germline epitopes (GL-MTV) identified by immunopeptidomics, another set based on mutated epitopes (Mutated-MTV) predicted by whole exome sequencing and a last set combines both germline and mutated epitopes (Mix-MTV). Our results demonstrate that both germline and mutated epitopes induced protection but the best therapeutic effect was achieved with the combination of both. Our platform is based on Cu-free click chemistry used for peptide-VLP coupling, thus enabling bedside production of a personalized cancer vaccine, ready for clinical translation.

Keywords:

virus-like particles, vaccine, personalized, melanoma, neoantigen, mutated, germline

Citation:

Mohsen MO, Vogel M, Riether C, Muller J, Salatino S, Ternette N, Gomes AC, Cabral-Miranda G, El-Turabi A, Ruedl C, Kundig TM, Dermime S, Knuth A, Speiser DE and Bachmann MF, Targeting Mutated Plus Germline Epitopes Confers Pre-clinical Efficacy of an Instantly Formulated Cancer Nano-Vaccine. *Frontiers Immunology*, 2019. 10:1015

Impact Factor: 5.511

Association of corneal nerve fiber measures with cognitive function in dementia

Georgios Ponirakis [1], Hanadi Al Hamad [2], Anoop Sankaranarayanan [3], Adnan Khan [1], Mani Chandran [2], Marwan Ramadan [2], Rhia Tosino [2], Priya Vitthal Gawhale [2], Maryam Alobaidi [2], Essa AlSulaiti [2], **Ahmed Elsotouhy** [4], Marwa Elorrabi [2], Shafi Khan [2], Navas Nadukkandiyil [2], Susan Osman [2], Noushad Thodi [5], Hamad Almuhannadi [1], Hoda Gad [1], Ziyad R Mahfoud [1], Fatima Al-Shibani [1], Ioannis N Petropoulos [1], **Ahmed Own** [4], Maryam Al Kuwari [2], **Ashfaq Shuaib** [6 7], Rayaz A Malik [1]

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Abstract

Objectives: Corneal confocal microscopy (CCM) is a noninvasive ophthalmic technique that identifies corneal nerve degeneration in a range of peripheral neuropathies and in patients with multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis. We sought to determine whether there is any association of corneal nerve fiber measures with cognitive function and functional independence in patients with MCI and dementia.

Methods: In this study, 76 nondiabetic participants with MCI (n = 30), dementia (n = 26), and healthy age-matched controls (n = 20) underwent assessment of cognitive and physical function and CCM.

Results: There was a progressive reduction in corneal nerve fiber density (CNFD), branch density (CNBD), and fiber length (CNFL) ($P < 0.0001$) in patients with MCI and dementia compared to healthy controls. Adjusted for confounders, all three corneal nerve fiber measures were significantly associated with cognitive function ($P < 0.05$) and functional independence ($P < 0.01$) in MCI and dementia. The area under the ROC curve to distinguish MCI with CNFD, CNBD, and CNFL was 69.1%, 73.2%, and 73.0% and for dementia it was 84.8%, 84.2%, and 86.2%, respectively.

Interpretation: CCM demonstrates corneal nerve fiber loss, which is associated with a decline in cognitive function and functional independence in patients with MCI and dementia.

Citation:

Ponirakis G, Al Hamad H, Sankaranarayanan A, Khan A, Chandran M, Ramadan M, Tosino R, Gawhale PV, Alobaidi M, AlSulaiti E, Elsotouhy A, Elorrabi M, Khan S, Nadukkandiyil N, Osman S, Thodi N, Almuhannadi H, Gad H, Mahfoud ZR, Al-Shibani F, Petropoulos IN, Own A, Al Kuwari M, Shuaib A, Malik RA. Association of corneal nerve fiber measures with cognitive function in dementia. *Annals of Clinical and Translational Neurology,*2019;6(4):689-697.

Impact Factor: 4.870

The association of PD-L1 expression with the efficacy of antiPD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials

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Abstract

Background: We conducted a meta-analysis to evaluate the efficacy of anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) monotherapy or immunotherapy combined with chemotherapy and further estimated the value of PD-L1 expression in predicting the response from anti-PD-1/PD-L1 treatments as monotherapy or in combination with chemotherapy. **Methods:** Clinical trial data were searched from electronic databases, which evaluated PD-1/PD-L1 inhibitors in non-small cell lung cancer (NSCLC) and correlated with PD-L1 expression levels. **Results:** Fifteen randomized-controlled trials involving 10,074 patients were identified. Comparing anti-PD-1/PD-L1 monotherapy to chemotherapy, the pooled HR for overall survival (OS) was 0.77 (95% CI: 0.69–0.85, P<0.00001). Subgroup analyses revealed that patients had longer OS at ≥1%, ≥5%, ≥10% and ≥50% PD-L1 expression levels. Patients with higher PD-L1 expression may get increased benefit from PD-1/PD-L1 inhibitors. Moreover, patients with PD-L1 ≥50% had an objective response rate (ORR) improvement from anti-PD-1/PD-L1 therapy (RR =1.87, 95% CI: 1.27–2.75, P=0.001), but no ORR benefits were observed

in patients with PD-L1 expression <1% (RR =0.82, 95% CI: 0.56–1.22, P=0.33) or 1–49% (RR =0.80, 95% CI: 0.64–0.98, P=0.03). OS was significantly better in patients receiving second- or-third line treatments (P<0.00001) with PD-L1 ≥1%. The efficacy of PD-1 inhibitors was similar to that of PD-L1 inhibitors, with no significant difference (P=0.63, I^2=0%). Furthermore, immunotherapy combined with chemotherapy had better OS (HR =0.64, 95% CI: 0.48–0.84, P=0.001) than chemotherapy alone. Subgroup analyses showed that patients benefited from the combined chemo-IO treatment in the first-line setting regardless of PD-L1 expression level. Conclusions: PD-L1 expression may be a valuable predictor of the efficacy of anti-PD-1/PD-L1 monotherapy in certain NSCLC patients. However, the combination of chemotherapy plus immunotherapy significantly improved survival regardless of the PD-L1 expression level in the first-line treatment of NSCLC.

Keywords:

Immunotherapy; meta-analysis; non-small cell lung cancer (NSCLC); programmed cell death ligand 1 (PD-L1)

Citation:

Xu Y, Wan B, Chen X, et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. *Translational Lung Cancer Research,* 2019;8(4):413-428.

Impact Factor: 4.806

Greensporone A, a Fungal Secondary Metabolite Suppressed Constitutively Activated AKT via ROS Generation and Induced Apoptosis in Leukemic Cell Lines

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Abstract

Greensporone A is a fungal secondary metabolite that has exhibited potential in vitro for anti-proliferative activity in vitro. We studied the anticancer activity of greensporone A in a panel of leukemic cell lines. Greensporone A-mediated inhibition of proliferation is found to be associated with the induction of apoptotic cell death. Greensporone A treatment of leukemic cells causes inactivation of constitutively activated AKT and its downstream targets, including members GSK3 and FOXO1, and causes downregulation of antiapoptotic genes such as Inhibitor of Apoptosis (IAPs) and Bcl-2. Furthermore, Bax, a proapoptotic member of the Bcl-2 family, was found to be upregulated in leukemic cell lines treated with greensporone A. Interestingly, gene silencing of AKT using AKT specific siRNA suppressed the expression of Bcl-2 with enhanced expression of Bax. Greensporone A-mediated increase in Bax/Bcl-2 ratio causes permeabilization of the mitochondrial membrane leading to the accumulation of cytochrome c in the cytoplasm. Greensporone A-induced cytochrome c accumulation causes the activation of caspase cascade and cleavage of its effector, poly (ADP-ribose) polymerase (PARP), leading to apoptosis. Greensporone A-mediated apoptosis in leukemic cells occurs through the generation of reactive oxygen species (ROS) due to depletion of glutathione (GSH) levels. Finally, greensporone A potentiated the anticancer activity

of imatinib in leukemic cells. In summary, our study showed that greensporone A suppressed the growth of leukemic cells via induction of apoptotic cell death. The apoptotic cell death occurs by inhibition of AKT signaling and activation of the intrinsic apoptotic/caspase pathways. These results raise the possibility that greensporone A could be developed as a therapeutic agent for the treatment of leukemia and other hematological malignancies.

Keywords:

AKT; apoptosis; cIAP; greensporone A; imatinib; reactive oxygen species

Citation:

Prabhu KS, Siveen KS, Kuttikrishnan S, Jochebeth A, Ali TA, Elareer NR, Iskandarani A, Quaiyoom Khan A, Merhi M, Dermime S, El-Elimat T, Oberlies NH, Alali FQ, Steinhoff M, Uddin S. Greensporone A, a Fungal Secondary Metabolite Suppressed Constitutively Activated AKT via ROS Generation and Induced Apoptosis in Leukemic Cell Lines. *Biomolecules.* 2019; 9(4):126.

Impact Factor: 4.694

Metformin Induces Different Responses in Clear Cell Renal Cell Carcinoma Caki Cell Lines.

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Abstract

Clear cell renal cell carcinoma (ccRCC) is the most common and lethal form of urological cancer diagnosed globally. Mutations of the von Hippel-Lindau (VHL) tumor-suppressor gene and the resultant overexpression of hypoxia-inducible factor (HIF)-1∂ protein are considered hallmarks of ccRCC. Persistently activated HIF-1α is associated with increased cell proliferation, angiogenesis, and epithelial¯mesenchymal transition (EMT), consequently leading to ccRCC progression and metastasis to other organs. However, the VHL status alone cannot predict the differential sensitivity of ccRCC to cancer treatments, which suggests that other molecular differences may contribute to the differential response of ccRCC cells to drug therapies. In this study, we investigated the response to metformin (an antidiabetic drug) of two human ccRCC cell lines Caki-1 and Caki-2, which express wild-type VHL. Our findings demonstrate a differential response between the two ccRCC cell lines studied, with Caki-2 cells being more sensitive to metformin compared to Caki-1 cells, which could be linked to the differential expression of HIF-1 despite both cell lines carrying a wild-type VHL. Our study unveils the therapeutic potential of metformin to inhibit the progression of ccRCC in vitro. Additional preclinical and clinical studies are required to ascertain the therapeutic efficacy of metformin against ccRCC.

Keywords:

AMP-activated kinase; hypoxia-inducible factor; metformin; renal cell carcinoma; von Hippel-Lindau

Citation:

Pasha, M., Sivaraman, S. K., Frantz, R., Agouni, A., & Munusamy, S. (2019). Metformin Induces Different Responses in Clear Cell Renal Cell Carcinoma Caki Cell Lines. *Biomolecules*, 2019, 9(3), 113

Impact factor: 4.694

Immune Checkpoints in Circulating and Tumor-Infiltrating CD4+ T Cell Subsets in Colorectal Cancer Patients

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Abstract

Blockade of inhibitory immune checkpoints (ICs) is a promising therapeutic approach; however, it has shown limited success in some cancers including colorectal cancer (CRC). The tumor microenvironment (TME) is largely responsible for response to therapy, and its constituents may provide robust biomarkers for successful immunotherapeutic approaches. In this study, we performed phenotypical characterization and critical analyses of key inhibitory ICs and T regulatory cell (Treg)-related markers on $CD4^+$ T cell subsets in CRC patients, and compared with normal colon tissues and peripheral blood from the same patients. We also investigated correlations between the levels of different $CD4^+$ T cell subsets and the clinicopathologic features including disease stage and tumor budding. We found a significant increase in the levels of $CD4^+FoxP3^+Helios^+$ T cells, which represent potentially highly immunosuppressive Tregs, in the CRC TME. Additionally, tumor-infiltrating $CD4^+$ T cells upregulated programmed cell death protein-1 (PD-1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), T cell immunoglobulin and mucin domain-3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3). We also characterized the expression of PD-1, CTLA-4, TIM-3, and LAG-3 on different $CD4^+FoxP3^{-/+}Helios^{-/+}$ T cell subsets. Interestingly, we found that CTLA-4, TIM-3, and LAG-3 were mainly co-expressed on $FoxP3^+Helios^+$ Tregs in the TME. Additionally, $FoxP3^{high}$ Tregs expressed higher levels of Helios, CTLA-4 and TIM-3 than $FoxP3^{low}$ T cells. These results highlight the significance of Tregs in the CRC TME and suggest that Tregs may hamper response to IC blockade in CRC patients, but effects of different IC inhibition regimes on Treg levels or activity warrants further investigations. We also found that $CD4^+CTLA\text{-}4^+$ T cells in circulation are increased in patients with advanced disease stage. This study simultaneously provides important insights into the differential levels of $CD4^+$ T cell subpopulations and IC expression in CRC TME, compared to periphery and associations with clinicopathologic features, which could be used as potential biomarkers for CRC progression and response to therapy.

Keywords:

colorectal cancer, T regulatory cells, immune checkpoints, tumor microenvironment, T cells

Citation:

Toor, S. M., Murshed, K., Al-Dhaheri, M., Khawar, M., Abu Nada, M., & Elkord, E. Immune Checkpoints in Circulating and Tumor-Infiltrating CD4+ T Cell Subsets in Colorectal Cancer Patients. *Frontiers in immunology*, 2019, 10, 2936.

Impact Factor: 4.530

In silico and in vivo models for Qatari-specific classical homocystinuria as basis for development of novel therapies

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Abstract

Homocystinuria is a rare inborn error of methionine metabolism caused by cystathionine ß-synthase (CBS) deficiency. The prevalence of homocystinuria in Qatar is 1:1,800 births, mainly due to a founder Qatari missense mutation, c.1006C>T; p.R336C (p.Arg336Cys). We characterized the structure-function relationship of the p.R336C-mutant protein and investigated the effect of different chemical chaperones to restore p.R336C-CBS activity using three models: in silico, ΔCBS yeast, and CRISPR/Cas9 p.R336C knock-in HEK293T and HepG2 cell lines. Protein modeling suggested that the p.R336C induces severe conformational and structural changes, perhaps influencing CBS activity. Wild-type CBS, but not the p.R336C mutant, was able to restore the yeast growth in ΔCBS-deficient yeast in a complementation assay. The p.R336C knock-in HEK293T and HepG2 cells decreased the level of CBS expression and reduced its structural stability; however, treatment of the p.R336C knock-in HEK293T cells with betaine, a chemical chaperone, restored the stability and tetrameric conformation of CBS, but not its activity. Collectively, these results indicate that the p.R336C mutation has a deleterious effect on CBS structure, stability, and activity, and using the chemical chaperones approach for treatment could be ineffective in restoring p.R336C CBS activity.

Keywords:

CBS; Homocystinuria; Qatar; chemical chaperones; in silico; in vivo models; p.R336C mutation

Citation:

Ismail, HM, Krishnamoorthy, N, Al-Dewik, N, Zayed, H, Mohamed, NA, Giacomo, VD, Gupta, S, Häberle, J, Thöny, B, Blom, HJ, Kruger, WD, Ben-Omran, T & Nasrallah, GK, 'In silico and in vivo models for Qatari-specific classical homocystinuria as basis for development of novel therapies', *Human Mutation*. 2019 F;40(2):230-240

Impact Factor: 4.453

Genetic Variation in CCL5 Signaling Genes and Triple Negative Breast Cancer: Susceptibility and Prognosis Implications

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Abstract

Triple-negative breast cancer (TNBC) accounts for ~15–20% of breast cancer (BC) and has a higher rate of early relapse and mortality compared to other subtypes. The Chemokine (C-C motif) ligand 5 (CCL5) and its signaling pathway have been linked to TNBC. We aimed to investigate the susceptibility and prognostic implications of genetic variation in CCL5 signaling genes in TNBC in the present study. We characterized variants in CCL5 and that of six other CCL5 signaling genes (CCND1, ZMIZ1, CASP8, NOTCH2, MAP3K21, and HS6ST3) among 1,082 unrelated Tunisian subjects (544 BC patients, including 196 TNBC, and 538 healthy controls), assessed the association of the variants with BC-specific overall survival (OVS) and progression-free survival (PFS), and correlated CCL5 mRNA and serum levels with CCL5 genotypes. We found a highly significant association between the CCND1 rs614367-TT genotype (OR = 5.14; P = 0.004) and TNBC risk and identified a significant association between the rs614367-T allele and decreased PFS in TNBC. A decreased risk of lymph node metastasis was associated with the MAP3K21 rs1294255-C allele, particularly in rs1294255-GC (OR = 0.47; P = 0.001). CCL5 variants (rs2107538 and rs2280789) were linked to CCL5 serum and mRNA levels. In the TCGA TNBC/Basal-like cohort the MAP3K21 rs1294255-G allele was associated with a decreased OVS. High expression of CCL5 in breast tumors was significantly associated with an increased OVS in all BC

patients, but particularly in TNBC/Basal-like patients. In conclusion, genetic variation in CCL5 signaling genes may predict not only TNBC risk but also disease aggressiveness.

Keywords:

CCL5, CCL5 signaling genes, triple negative breast cancer, prognosis, susceptibility

Citation:

han J, Chouchane A, Mokrab Y, Saad M, Boujassoum S, Sayaman RW, Ziv E, Bouaouina N, Remadi Y, Gabbouj S, Roelands J, Ma X, Bedognetti D and Chouchane L, Genetic Variation in CCL5 Signaling Genes and Triple Negative Breast Cancer: Susceptibility and Prognosis Implications. *Frontiers in Oncology*. 2019, 9:1328

Impact Factor: 4.137

Expression and Function of the Endocannabinoid Modulating Enzymes Fatty Acid Amide Hydrolase and *N*-Acylphosphatidylethanolamine-Specific Phospholipase D in Endometrial Carcinoma

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Abstract

Background: The concentrations of three *N*-acylethanolamines (NAEs), anandamide (AEA), *N*-oleoylethanolamide (OEA), and *N*-palmitylethanolamide (PEA) are increased in the endometria of women with endometrial cancer (EC). It is widely accepted that plasma levels of these three NAEs are regulated by the actions of the rate-limiting enzymes *N*-acylphoshatidylethanolamine-specific phospholipase D (NAPE-PLD) and fatty acid amide hydrolase (FAAH), which are synthesizing and degradative, respectively. The expression and activity of these enzymes have not previously been studied in EC. Methods: FAAH activity in peripheral blood lymphocytes, and transcript and protein expression for FAAH and NAPE-PLD in EC tissues were measured using enzyme, quantitative RT-PCR, and histomorphometry (of immunoreactive tissue sections), respectively. Samples were from 6 post-menopausal women with atrophic endometria (controls) and 34 women with histologically diagnosed EC. Concentrations of the three NAEs also measured in plasma and tissues were correlated with lymphocytic FAAH activity and the NAPE-PLD and FAAH transcript and protein levels. Results: Peripheral lymphocyte FAAH activity was unaffected in women with EC compared to controls. The FAAH transcript expression level was significantly ($p < 0.0001$) 75% lower in EC whilst NAPE-PLD levels were not significantly ($p = 0.798$) increased. In line with the transcript data, a significant ($p < 0.0001$) tumor type-dependent 70-90% decrease in FAAH protein and significant 4- to 14-fold increase in NAPE-PLD protein ($p < 0.0001$) was observed in the malignant tissue with more advanced disease having lower FAAH and higher

NAPE-PLD expression than less advanced disease. Correlation analyses also confirmed that tissue NAE concentrations were inversely related to FAAH expression and directly correlated to NAPE-PLD expression and the NAPE-PLD/FAAH ratio. Conclusion: These data support our previous observation of tissue levels of AEA, OEA, and PEA and a role for NAE metabolism in the pathogenesis of EC.

Keywords:

N-acylphoshatidylethanolmine-specific phospholipase D; endocannabinoids; endometrial cancer; fatty acid amide hydrolase; gene expression; immunohistochemistry

Citation:

Ayakannu T, Taylor AH, Bari M, Mastrangelo N, Maccarrone M, Konje JC1,6,7. (Expression and Function of the Endocannabinoid Modulating Enzymes Fatty Acid Amide Hydrolase and N-Acylphosphatidylethanolamine-Specific Phospholipase D in Endometrial Carcinoma. *Frontiers in Oncology,* 2019; 9. 1363.

Impact factor: 4.137

Sanguinarine Induces Apoptosis Pathway in Multiple Myeloma Cell Lines via Inhibition of the JaK2/STAT3 Signaling

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Abstract

Sanguinarine (SNG), a benzophenanthridine alkaloid, has displayed various anticancer abilities in several vivo and in vitro studies. However, the anticancer potential of SNG is yet to be established in multiple myeloma (MM), a mostly incurable malignancy of plasma cells. In this study, we aimed to investigate the potential anti-proliferative and pro-apoptotic activities of SNG in a panel of MM cell lines (U266, IM9, MM1S, and RPMI-8226). SNG treatment of MM cells resulted in a dose-dependent decrease in cell viability through mitochondrial membrane potential loss and activation of caspase 3, 9, and cleavage of PARP. Pre-treatment of MM cells with a universal caspase inhibitor, Z-VAD-FMK, prevented SNG mediated loss of cell viability, apoptosis, and caspase activation, confirming that SNG-mediated apoptosis is caspase-dependent. The SNG-mediated apoptosis appears to be resulted from suppression of the constitutively active STAT3 with a concomitant increase in expression of protein tyrosine phosphatase (SHP-1). SNG treatment of MM cells leads to down-regulation of the anti-apoptotic proteins including cyclin D, Bcl-2, Bclxl, and XIAP. In addition, it also upregulates pro-apoptotic protein, Bax. SNG mediated cellular DNA damage in MM cell lines by induction of oxidative stress through the generation of reactive oxygen species and depletion of glutathione. Finally, the subtoxic concentration of SNG enhanced the cytotoxic effects of anticancer drugs bortezomib (BTZ) by suppressing the viability of MM cells via induction of caspase-mediated apoptosis. Altogether our findings demonstrate that SNG induces mitochondrial and caspase-dependent apoptosis, generates oxidative stress, and suppresses MM cell lines proliferation. In addition, co-treatment of MM cell lines with sub-toxic doses of SNG and BTZ potentiated the cytotoxic activity. These results would suggest that SNG could be developed into therapeutic agent either alone or in combination with other anticancer drugs in MM.

Keywords:

STAT3; apoptosis; caspases; hematological malignancy; multiple myeloma; sanguinarine

Citation:

Akhtar S, Achkar IW, Siveen KS, Kuttikrishnan S, Prabhu KS, Khan AQ, Ahmed EI, Sahir F, Jerobin J, Raza A, Merhi M, Elsabah HM, Taha R, Omri HE, Zayed H, Dermime S, Steinhoff M, Uddin S. Sanguinarine Induces Apoptosis Pathway in Multiple Myeloma Cell Lines via Inhibition of the JaK2/STAT3 Signaling. *Frontiers in Oncology*, 2019; 9:285.

Impact Factor: 4.137

Curcumin Induces Apoptotic Cell Death via Inhibition of PI3-Kinase/AKT Pathway in B-Precursor Acute Lymphoblastic Leukemia

Shilpa Kuttikrishnan [1], Kodappully S Siveen [1], Kirti S Prabhu [1], Abdul Quaiyoom Khan [1], Eiman I Ahmed [1], Sabah Akhtar [1], Tayyiba A Ali [1], Maysaloun Merhi [2], Said Dermime [2], Martin Steinhoff [1,3,4,5], Shahab Uddin [1]

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Abstract

Acute lymphoblastic leukemia (ALL) is a significant cancer of children resulting from the clonal proliferation of lymphoid precursors with arrested maturation. Although chemotherapeutic approaches have been achieving successful remission for the majority of cases of childhood ALL, development of resistance to chemotherapy has been observed. Thus, new therapeutic approaches are required to improve patient's prognosis. Therefore, we investigated the anticancer potential of curcumin in ALL. We tested a panel of B-precursor ALL (B-Pre-ALL) cell lines with various translocations after treatment with different doses of curcumin. Curcumin suppresses the viability in a concentration-dependent manner in 697, REH, SupB15, and RS4;11 cells (doses from 0 to 80 μM). Curcumin induces apoptosis in B-Pre-ALL cell lines via activation of caspase-8 and truncation of BID. Curcumin treatment increased the ratio of Bax/Bcl-2 and resulted in a leaky mitochondrial membrane that led to the discharge of cytochrome c from the mitochondria to the cytoplasm, the activation of caspase 3 and the cleavage of PARP. Curcumin treatment of B-Pre-ALL cell lines induced a dephosphorylation of the constitutive phosphorylated AKT/PKB and a down-regulation of the expression of cIAP1, and XIAP. Moreover, curcumin mediates its anticancer activity by the generation of reactive oxygen species. Finally, the suboptimal doses of curcumin potentiated the anticancer activity of cisplatin. Altogether, these results suggest an important therapeutic role of curcumin, acting as a growth suppressor of B-Pre-ALL by apoptosis via inactivation of AKT/PKB and down-regulation of IAPs and activation of intrinsic apoptotic pathway via generation of Reactive Oxygen Species (ROS). Our interesting findings raise the possibility of considering curcumin as a potential therapeutic agent for the treatment of B-Pre-ALL.

Keywords:

B-Pre-ALL cells; ROS; apoptosis; curcumin; signaling

Citation:

Kuttikrishnan S, Siveen KS, Prabhu KS, Khan AQ, Ahmed EI, Akhtar S, Ali TA, Merhi M, Dermime S, Steinhoff M, Uddin S. Curcumin Induces Apoptotic Cell Death via Inhibition of PI3-Kinase/AKT Pathway in B-Precursor Acute Lymphoblastic Leukemia. *Frontiers in Oncology*, 2019;9:484.

Impact Factor: 4.137

Evaluation of cationic channel TRPV2 as a novel biomarker and therapeutic target in Leukemia-Implications concerning the resolution of pulmonary inflammation

Kodappully S. Siveen[1], Kirti S. Prabhu[1], Aeijaz S. Parray[1], Maysaloun Merhi[2], Abdelilah Arredouani[3], Mohamed Chikri[3], **Shahab Uddin[1], Said Dermime[2]**, Ramzi M. Mohammad[4], **Martin Steinhof[1]**, Ibrahim A. Janahi[5], **Fouad Azizi[1]**

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Abstract

Patients treated during leukemia face the risk of complications including pulmonary dysfunction that may result from infiltration of leukemic blast cells (LBCs) into lung parenchyma and interstitium. In LBCs, we demonstrated that transient receptor potential vanilloid type 2 channel (TRPV2), reputed for its role in inflammatory processes, exhibited oncogenic activity associated with alteration of its molecular expression profile. TRPV2 was overexpressed in LBCs compared to normal human peripheral blood mononuclear cells (PBMCs). Additionally, functional full-length isoform and nonfunctional short form pore-less variant of TRPV2 protein were up-regulated and down-regulated respectively in LBCs. However, the opposite was found in PBMCs. TRPV2 silencing or pharmacological targeting by Tranilast (TL) or SKF96365 (SKF) triggered caspace-mediated apoptosis and cell cycle arrest. TL and SKF inhibited chemotactic peptide fMLP-induced response linked to TRPV2 Ca2+ activity, and down-regulated expression of surface marker CD38 involved in leukemia and lung airway inflammation. Challenging lung airway epithelial cells (AECs) with LBCs decreased (by more than 50%) transepithelial resistance (TER) denoting barrier function alteration. Importantly, TL prevented such loss in TER. Therefore, TRPV2 merits further exploration as a pharmacodynamic biomarker for leukemia patients (with pulmonary inflammation) who might be suitable for a novel [adjuvant] therapeutic strategy based on TL.

Citation:

Siveen, KS, Prabhu, KS, Parray, AS, Merhi, M, Arredouani, A, Chikri, M, Uddin, S, Dermime, S, Mohammad, RM, Steinhoff, M, Janahi, IA & Azizi, F, 'Evaluation of cationic channel TRPV2 as a novel biomarker and therapeutic target in Leukemia-Implications concerning the resolution of pulmonary inflammation', *Scientific Reports*, 2019; 9:1554.

Impact Factor: 4.011

Oral Cancer Knowledge, Attitude, and Practice of Dentists in the State of Qatar

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Abstract

Objectives: The aim of this study was to assess existing knowledge on oral cancer (OC), attitude toward OC examination, and clinical practice among dentists practicing in the governmental health sector in the State of Qatar, including the influence of personal characteristics.

Materials and methods: All 271 dentists practicing in Primary Health Care Centers (PHCC) and the Hamad Medical Corporation (HMC) were invited to participate in this cross-sectional study. Of these, 177 completed a self-administered, 48-item questionnaire. Based on the responses, knowledge of the risk factors for and clinical presentation of OC was categorized as high, medium, or low, and then further separated into satisfactory (medium/high) and unsatisfactory (low). Information on attitudes toward OC examination and clinical practice was also taken from the questionnaire.

Results: The mean score for knowledge of the clinical presentation of OC was 7.59 (standard deviation [SD] = 2.40) out of 14. The mean score for knowledge of the risk factors for OC was 8.96 (SD = 2.31) out of 16. Dentists with ≤10 years of experience were more likely to have satisfactory knowledge of OC compared to dentists with >15 years of experience. Attending a continuous professional development (CPD) course on OC showed a trend with satisfactory clinical knowledge, although it was not statistically significant.

Conclusion: This study identified gaps in dentists' knowledge of OC; dentists demonstrated unsatisfactory knowledge of the clinical presentation of and risk factors for OC. The findings highlighted the need for educational interventions on OC, which are essential to improving health care outcomes and delivery of care.

Keywords:

Qatar; attitude; continuous professional development courses; dentists; knowledge; oral cancer; practice

Citation:

Jboor, D. H., Al-Darwish, M. S., & Nur, U. Oral Cancer Knowledge, Attitude, and Practice of Dentists in the State of Qatar. *Dentistry journal*, 2019,7(2), 43.

Impact Factor: 3.28

Efficacy of selective digestive decontamination in patients with multiple myeloma undergoing high-dose chemotherapy and autologous stem cell transplantation.

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Abstract

Selective digestive decontamination (SDD) with the oral, non-absorbable antimicrobial substances gentamicin, vancomycin and amphotericin B was optionally used at our institution to reduce the risk of gastrointestinal tract derived infections in multiple myeloma (MM) patients undergoing high-dose chemotherapy with subsequent autologous stem cell transplantation (HDCT/ASCT). The majority of patients received sulfamethoxazole-trimethoprim as pneumocystis pneumonia prophylaxis. From 203 patients receiving their first HDCT/ASCT between 2009 and 2015, we compared retrospectively 90 patients receiving SDD to 113 patients not receiving SDD. The administration of SDD was associated with a reduction of bacterial infections after HDCT/ASCT (overall: 8% versus 24%, p = .002; gram-negative pathogens: 1% versus 11%, p = .006) and less use of systemic antibiotics (62% versus 77%, p = .022). Omission of SDD was an independent risk factor for developing neutropenic fever and bloodstream infections. SDD could be an option to reduce bacterial infections in patients undergoing HDCT/ASCT that needs to be tested in prospective trials.

Keywords:

Infectious complications; antibiotic resistance; autologous stem cell transplantation; myeloma; neutropenic fever; selective digestive decontamination

Citation:

Mürner, Céline M; Stenner-Liewen, Frank; Seifert, Burkhardt; Mueller, Nicolas J; Schmidt, Adrian; Renner, Christoph; Schanz, Urs; Knuth, Alexander; Manz, Markus G; Scharl, Michael; Gerber, Bernhard; Samaras, Panagiotis. Efficacy of selective digestive decontamination in patients with multiple myeloma undergoing high-dose chemotherapy and autologous stem cell transplantation. *Leukemia & Lymphoma*, 2019, 60(3):685-695.

Impact Factor: 2.674

Sanguinarine suppresses growth and induces apoptosis in childhood acute lymphoblastic leukemia

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Abstract

Sanguinarine (Sang), a plant-derived compound isolated from the roots of Sanguinaria canadensis was evaluated for its potential pro-apoptotic effects in precursor B acute lymphoblastic leukemia (Pre-ALL) cell lines. Treatment of 697, REH, RS4;11, and SupB15 cell lines with Sang exhibited significant inhibition of cell viability via induction of apoptotic cell death. Sang-mediated apoptosis was found to be associated with the increased expression of proapoptotic bax with concomitant decrease of Bcl-2 expression leading to depolarization of mitochondria membrane resulting in loss of mitochondrial membrane potential (MMP). The reduced MMP caused the leakage in mitochondrial membrane and release of cytochrome c into the cytosol. The cytochrome c then mediates the activation of caspase-cascade and subsequently PARP cleavage. Furthermore, pretreatment with z-VAD-FMK, a pan-caspase inhibitor, abrogated Sang-induced inhibition of cell viability, induction of apoptosis. Sang treatment also reduced the phosphorylation of AKT and suppressed the expression of a number of anti-apoptotic genes such as cIAP1, cIAP2, and XIAP. Sang mediates its anti-cancer activity by generation of reactive oxygen species (ROS) due to depletion of glutathione level in leukemic cell lines. Pretreatment of these cells with N-acetyl cysteine (NAC) prevented Sang-induced depletion of glutathione level and mitochondrial-caspase-induced apoptosis. Finally, Sang treatment of Pre-ALL cell suppressed colony formation ability of these cells suggesting Sang has an anti-leukemic potential. Altogether, our data suggest that Sang is an efficient inducer of intrinsic apoptotic cell death via generation of ROS and exhibition of anti-leukemic effect in Pre-ALL cells raises the possibility to develop Sang as a therapeutic modality for the treatment and management of Pre-ALL.

Keywords:

Apoptosis; ROS; pre-ALL cells; sanguinarine; signaling

Citation:

S. Kuttikrishnan, K. S. Siveen, Kirti S. Prabhu, Abdul Quaiyoom Khan, Sabah Akhtar, Jericha M. Mateo, Maysaloun Merhi, Ruba Taha, Halima El Omri, Fatima Mraiche, Said Dermime & Shahab Uddin, Sanguinarine suppresses growth and induces apoptosis in childhood acute lymphoblastic leukemia, *Leukemia & Lymphoma,* 2019 , 60:3, 782-794

Impact Factor: 2.674

Clinical Profiles of Selected Biomarkers Identifying Infection and Cancer Patients: A Gorzów Hospital Example

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Abstract

Introduction. Many pathobiological processes that manifest in a patient's organs could be associated with biomarker levels that are detectable in different human systems. However, biomarkers that promote early disease diagnosis should not be tested only in personalized medicine but also in large-scale diagnostic evaluations of patients, such as for medical management. *Objective*. We aimed to create an easy algorithmic risk assessment tool that is based on obtainable "everyday" biomarkers, identifying infection and cancer patients. *Patients*. We obtained the study data from the electronic medical records of 517 patients (186 infection and 331 cancer episodes) hospitalized at Gorzów Hospital, Poland, over a one and a half-year period from the 1st of January 2017 to the 30th of June 2018. *Methods and Results*. A set of consecutive statistical methods (cluster analysis, ANOVA, and ROC analysis) was used to predict infection and cancer. For in-hospital diagnosis, our approach showed independent clusters of patients by age, sex, MPV, and disease fractions. From the set of available "everyday" biomarkers, we established the most likely bioindicators for infection and cancer together with their classification cutoffs. *Conclusions*. Despite infection and cancer being very different diseases in their clinical characteristics, it seems possible to discriminate them using "everyday" biomarkers and popular statistical methods. The estimated cutoffs for the specified biomarkers can be used to allocate patients to appropriate risk groups for stratification purposes (medical management or epidemiological administration).

Citation:

Brzeźniakiewicz-Janus K., Lancé M. D, Tukiendorf A., Franków M., Rupa-Matysek J., Wolny-Rokicka E., Gil L. Clinical Profiles of Selected Biomarkers Identifying Infection and Cancer Patients: A Gorzów Hospital Example, *Disease Markers Volume* 2019, 8 pages

Impact Factor: 2.560

Effect of denosumab versus zoledronic acid on calcium levels in cancer patients with bone metastasis: A retrospective cohort study.

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Abstract

Objective: To identify the incidence of hypercalcemia and hypocalcemia in zoledronic acid and denosumab groups. Secondary objective was to determine the correlation between calcium supplement and calcium level control.

Methods: An observational retrospective cohort study was conducted by reviewing patient electronic records, laboratory results, and medication charts from 1 August 2015 to 31 July 2016. Adult cancer patients who were diagnosed with bone metastasis secondary to a solid tumor or multiple myeloma and who received either zoledronic acid or denosumab were included. Other indications for bone targeting agents were excluded. Data of bone targeting agents administration encounters were collected, evaluated, and analyzed.

Results: A total of 1141 encounters (for 271 patients) were included. The incidence of hypocalcemia was higher in denosumab compared to zoledronic acid group (5.5% vs. 3.1%, OR = 0.55, 95% CI [0.3-1.0]; P = 0.05). Hypercalcemia incidence was also higher in denosumab group (8.5% vs. 3.1%, OR = 2.9, 95% CI [1.68-5.03]; P < 0.0001). Breast cancer was the most common malignancy associated with hypocalcemia (27.3%) followed by ovarian cancer (25%) and multiple myeloma (22.7%). The risk of developing hypocalcemia was reduced by 16% in patients receiving calcium supplementation (RR = 0.84, 95% CI [0.55-1.20]; P = 0.39).

Conclusion: Denosumab use was associated with higher rates of both hypercalcemia and hypocalcemia compared to zoledronic acid. Adequate supplementation with calcium substantially reduced the risk of hypocalcemia. Our results highlight the importance of taking preventative measures upon bone targeting agents initiation and during treatment including regular monitoring of calcium levels and providing supplements accordingly.

Keywords:

Denosumab; bone metastasis; cancer; hypocalcemia; zoledronic acid

Citation:

S. M. Nasser, A. Sahal, A. Hamad, S. Elazzazy*, "Effect of denosumab versus zoledronic acid on calcium levels in cancer patients with bone metastasis: A retrospective cohort study", *Journal of Oncology Pharmacy Practice*, 2019. 25(8):1846-1852.

Impact Factor: 2.42

Clinical exome sequencing in 509 Middle Eastern families with suspected Mendelian diseases: The Qatari experience

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Abstract

Background: Clinical exome sequencing (CES) is rapidly becoming the diagnostic test of choice in patients with suspected Mendelian diseases especially those that are heterogeneous in etiology and clinical presentation. Reporting large CES series can inform guidelines on best practices for test utilization and improves accuracy of variant interpretation through clinically-oriented data sharing.

Methods: This is a retrospective series of 509 probands from Qatar who underwent singleton or trio CES either as a reflex or naïve (first tier) test from April 2014 to December 2016 for various clinical indications.

Results: The CES diagnostic yield for the overall cohort was 48.3% (n = 246). Dual molecular diagnoses were observed in 2.1% of cases; nearly all of whom (91%) were consanguineous. We report compelling variants in 11 genes with no established Mendelian phenotypes. Unlike reflex-WES, naïve WES was associated with a significantly shorter diagnostic time (3 months vs. 18 months, $p < 0.0001$).

Conclusion: Middle Eastern patients tend to have a higher yield from CES than outbred populations, which has important implications in test choice especially early in the diagnostic process. The relatively high diagnostic rate is likely related to the predominance of recessive

diagnoses (60%) since consanguinity and positive family history were strong predictors of a positive CES.

Key words:

Arab; Mendelian diseases; Middle East; Qatar; clinical exome sequencing; consanguinit

Citation:

l-Dewik, N. & Mohd, H. & Al-Mureikhi, M. & Ali, R. & Al-Mesaifri, F. & Hashim, L. & Shahbeck, N. & El-Akouri, K. & Almulla, M. & Sulaiman, R. & Musa, S. & Al Nabet, A. & Richard, G. & Juusola, J. & Solomon, B. & Alkuraya, F. & Ben-Omran, T. Clinical exome sequencing in 509 Middle Eastern families with suspected Mendelian diseases: The Qatari experience. *American Journal of Medical Genetics* 2019;179A:927–935

Impact Factor: 2.197

A Hermeneutic Interpretation of Nurses' Experiences of Truth Telling and Harms in Cancer Care in Qatar

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Abstract

Background: Telling the truth to cancer patients remains under debate in the Middle East, where concealment about diagnosis and prognosis occurs in some cases. Concealment results in challenges for nurses providing care.

Objective: The aim of this study was to understand nurses' lived experiences of caring for cancer patients whose cancer diagnosis or prognosis has been withheld from them.

Methods: Eight nurses from the national cancer center in Qatar were interviewed. The transcripts of the interview texts were interpreted using Gadamer's hermeneutic approach.

Results: The interpretations are shaped by understandings of harm. Nurses assessed harm using empathy. Nurses' empathy was permeated with fears that accompany a cancer diagnosis; the language of cancer is interpreted as a language of fear. It is ideas about harms and evoking patients' fear that generates nurses' experiences of complexity, ambiguity, and conflicting feelings regarding truth telling and concealment. The meanings nurses drew from their experiences rested on understandings about love, vulnerability, and opportunities to atone. We interpret nurses' descriptions of being enmeshed in a web of lies through which multidimensional harms are experienced. The complexities of nurses' experiences go well beyond the universal concepts of informed consent and patients' rights.

Conclusions: Nurses' experiences reveal insights that likely resonate across other jurisdictions in the Arabic Gulf and other Eastern cultures, where nurses deal with these sensitive issues case by case.

Implications for Practice: Leaders and health professionals in cancer care in such cultures must establish more nuanced and transparent interdisciplinary approaches to respond to the complexities of truth telling in cancer care.

Keywords

Breaking bad news, Cancer, Nurses, Nurses' experience, Nondisclosure, Qatar, Truth telling

Citation:

Alsaadi WA, Rankin JM, Bylund CL., A Hermeneutic Interpretation of Nurses' Experiences of Truth Telling and Harms in Cancer Care in Qatar, *Cancer Nursing:* 2019; Volume 42 - Issue 6 - p 484-491

Impact Factor: 2.022

Perceptions and expectations of health care providers towards clinical pharmacy services at a tertiary cancer centre in Qatar.

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Abstract

Background: Clinical pharmacy services started in 2009 at the National Center for Cancer Care and Research, Qatar. Clinical pharmacy services were established to provide comprehensive prescription of drug management and support, and consulting services to build clinically efficient and cost-effective pharmacy program.

Aim: To determine perceptions and expectations of healthcare providers toward the clinical pharmacy services at the National Center for Cancer Care and Research.

Methods: A cross-sectional survey of healthcare providers was conducted from January to May 2018. A self-administered electronic/paper survey containing four domains assessing healthcare providers' perceptions and expectations towards clinical pharmacy services, perceived barriers to clinical pharmacist role and suggested area for improvement was sent to 375 healthcare providers including physicians, operational pharmacists, nurses and dietitians.

Results: The response rate was 112/375. Most of the healthcare providers (74%) perceived the increasing interest in clinical pharmacy services. Also, they expected (1) providing consultations regarding appropriate medication choices (82%); (2) providing information about medication availability and shortages (82%); (3) assisting in the prescribing of cost-effective drugs by providing pharmacogenomics information routinely (75%) and (4) Participating actively in research activities (74%). Overall, healthcare providers have a high level of trust in the clinical pharmacists' abilities ($P < 0.01$). Nurses were less appreciative ($P < 0.002$) of the positive role of clinical pharmacists in direct patient care as compared to both physicians and pharmacists (64.2%, 90% and 95.7%, respectively).

Conclusion: This study revealed a positive attitude towards the role of clinical pharmacists by healthcare providers at National Center for Cancer Care and Research. However, there is an area of improvement by empowering with privilege and staffing, elevating the awareness and expansion in the ambulatory care settings.

Keywords:

Perceptions; cancer; clinical pharmacy; expectations; healthcare providers; oncology

Citation:

N. H. Omar, S. Elazzazy, A. J Nashwan, Y. Eltorki, O. Abdallah, H. Afifi, N. Kassem, M. Yassin, A. Hamad, "Perceptions and Expectations of Health Care Providers towards Clinical Pharmacy Services at the Tertiary Cancer Center in Qatar.", JOPP, *Journal of Oncology Pharmacy Practice* 2019, 1–11, 72

Impact Factor: 1.826

Final Height and Endocrine Complications in Patients with β-Thalassemia Intermedia: Our Experience in Non-Transfused Versus Infrequently Transfused Patients and Correlations with Liver Iron Content

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Abstract

Background: β-thalassemia intermedia (TI) spans a wide spectrum of severity and carries higher morbidity than previously recognized, including extramedullary hematopoiesis, leg ulcers, gallstones, thrombosis, secondary heart failure, pulmonary hypertension, skeletal deformity, growth retardation and endocrine abnormalities, such as diabetes mellitus, hypothyroidism, osteoporosis, and hypogonadism.

Objectives: To evaluate the final height and the endocrine complications encountered in young adult patients with TI followed at Hematology Section, Doha (Qatar) in relation to liver iron content in non-transfused versus infrequently transfused TI patients.

Patients And Methods: This retrospective cohort study was performed on 28 young adults with TI who were randomly selected from the Hematology Clinic of the Hematology Section, National Centre for Cancer Care and Research, Hamad Medical Corporation of Doha (Qatar).Eligibility criteria for this retrospective analysis included TI patients diagnosed by complete blood count, hemoglobin electrophoresis and young adult age (≥ 18 years).Group 1 included nine patients who did not receive any blood transfusion, and Group 2 included 19 patients who infrequently received blood transfusions. Data recorded from charts included demographic characteristics (gender, date of birth, ethnicity), disease and treatment characteristics (e.g., transfusion frequency, history of chelation therapy, and splenectomy), auxological and pubertal data [growth percentiles and pubertal stages, and body mass index (BMI)], laboratory data and target organ complications (including endocrinopathies and liver disease). Iron overload was assessed by direct (liver iron content; LIC) and indirect methods (SF), and bone mass index (BMA) by dual-energy X-ray absorptiometry (DXA).

Results: Short stature [Final Height (Ht) SDS < -2] occurred in 25% of patients with no difference between the two groups of patients. Insulin growth factor 1 (IGF-1) SDS was low in 35.7 % of patients with no statistical difference among the two groups. Impaired fasting blood glucose occurred in 17.8% of patients, diabetes mellitus in 25% and hypogonadotropic hypogonadism in 10.7% of them. Morning cortisol was low in one patient. No thyroid or hypo-parathyroid abnormalities were detected in any patient. Liver iron content (LIC) > 15 mg/g dry weight and SF > 2,000 ng/mL were detected in 75% of the patients. The values resulted significantly higher in the transfused group (Group 2). High liver enzyme level (ALT) was detected in 42.8 % of patients, and the values were significantly higher in the transfused group (Group 2). Total and fetal Hb was significantly higher in group 1 versus group 2. Osteopenia was diagnosed in 14.3% of patients. Females had significantly better final height SDS, higher IGF-1 SDS, lower LIC and fasting blood glucose level compared to males. Significant correlations were found between Ht-SDS and IGF-1 SDS; LIC and SF, level; ALT and LIC, SF levels. Total and fetal Hb did not correlate significantly with Ht-SDS or IGF-1 level.

Conclusions: A significant number of TI patients have high LIC, short stature and endocrine disorders. Patients who require occasional transfusions have more liver iron overload and higher hepatic dysfunction. Females appear to attain a better final adult height and have higher IGF1-SDS versus males. Our data emphasize the need for long term surveillance for identification of organ-specific risk factors and early disease manifestations. We also recommend close monitoring of endocrine and other complications, according to the international guidelines.

Keywords:

Endocrine complications; Gender; Growth; IGF-1; Iron overload; Liver iron concentration; Serum ferritin; Thalassemia intermedia

Citation:

Yassin, M. A., Soliman, A. T., De Sanctis, V., Yassin, K. S., & Abdulla, M. A. Final Height and Endocrine Complications in Patients with β-Thalassemia Intermedia: Our Experience in Non-Transfused Versus Infrequently Transfused Patients and Correlations with Liver Iron Content. *Mediterranean journal of hematology and infectious diseases*, 2019, 11(1)

Impact Factor: 1.586

Gallbladder cancer: 7-Year experience from Qatar

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Abstract

Background: Gallbladder cancer (GC) is a relatively rare disease. To date, there are no studies describing the epidemiology of this disease in Qatar.Methods A retrospective analysis of the cases of GC in Hamad General Hospital in Qatar from 2009 to 2016.**Results:** Thirty-five patients presented with GC during the study period, 10 females (28.6%) and 25 males (71.4%). Fourteen patients (40%) were diagnosed incidentally after laparoscopic cholecystectomy, 16 (48.6%) were diagnosed pathologically, and 4 (11.4%) were diagnosed radiologically. The median age at diagnosis was 54 years (31–78). 74.3% of the disease occurred in patients less than 60 years old. Metastatic disease was discovered in 25 patients (71.4%) versus no metastasis in 10 patients (28.6%). The most common sites for metastasis were the liver (42.9%), peritoneum (25.7%), and lymph nodes (25.7%). Curative central hepatic resection was done in 8 patients (22.9%). Pathology showed adenocarcinoma in 27 patients (77.1%), neuroendocrine tumor in 3 patients (8.6%) and high-grade dysplasia in 1 patient (2.9%). No histopathology was available for 4 patients (11.4%). Twenty-eight patients (80.0%) had regular follow up, with 22 (62.9%) still alive. Six patients (17.1%) died during follow up with survival after diagnosis ranging from 42 days to 6.8 years. Conclusions In Qatar, due to the unique demographics, GC is more common in males and younger age groups. Most of the patients present late with metastasis, but curative resection is associated with long-term survival.

Keywords:

Gallbladder cancer, Epidemiology, Risk factors, Survival, Qatar

Citation:

Sulieman, I., El Moghazy, W., El Ansari, W., Elaffandi, A., Khalaf, H., (2019). Gallbladder cancer: 7-Year experience from Qatar. *Annals of medicine and surgery*, 2019. 44. 33-38.

Impact factor: 1.5

Hepatocellular Carcinoma in a Rapidly Growing Community: Epidemiology, Clinico-Pathology and Predictors of Extrahepatic Metastasis

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Abstract

Background and study aims: Hepatocellular carcinoma (HCC) with extrahepatic metastasis has been studied, however, data from the Middle East remain scarce. In this study, we assess epidemiology of HCC in Qatar, and identify predictors of the metastatic behaviour.

Patients and methods: All newly diagnosed HCC patients on top of liver cirrhosis between 2011 and 2015 were included in the study.

Results: A total of 180 patients met our inclusion criteria. The mean age was 58.8 ± 10.5 years with a mean follow-up of 1.0 ± 1.1 years. There were 150 male patients and HCV was the most common cause of liver cirrhosis 108 (60%), and 22 (12.2%) patients were classified as Child-Pugh class C. The overall survival of 51.1%, and 47 (26%) had at least one extrahepatic metastasis at the time of diagnosis. Single site metastasis was diagnosed in 10 patients, whereas 37 patients had multiple sites metastases. We compared patients who had metastases with patients who did not have metastasis at the time of diagnosis of HCC regarding several variables, and analysis revealed that tumour diameter larger than 5 cm (OR = 6.10, 95% CI = 1.85-20.12) (p = 0.003), and bilobar liver involvement (OR = 5.49, 95% CI = 1.10-27.30) (p = 0.037) were independent predictors of metastatic behaviour of HCC.

Conclusion:The incidence of HCC is rising in our population; extrahepatic metastasis is no longer rare and tumours larger than 5 cm and bilobar involvement are determinants of the extrahepatic metastasis.

Keywords:

Hepatocellular carcinoma; Incidence; Maximal tumour diameter; Metastasis; Prognosis; Risk factors; Total tumour volume.

Citation:

Elmoghazy W, Ahmed K, Vijay A, et al. Hepatocellular carcinoma in a rapidly growing community: Epidemiology, clinico-pathology and predictors of extrahepatic metastasis. Arab *Journal of Gastroenterology*. 2019;20(1):38-43.

Impact Factor: 0.75

Targeting Wnt/EZH2/microRNA-708 signaling pathway inhibits neuroendocrine differentiation in prostate cancer

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Abstract

Prostate cancer (PC) castration resistance has been linked to the differentiation of PC luminal cells into hormone refractory neuroendocrine (NE) cells. However, the molecular mechanisms controlling the emergence of lethal NE prostate cancer (NEPC) remain unclear. The present study aimed to investigate the mechanisms underlying the transition from prostate adenocarcinoma to NEPC. The microRNA miR-708 was involved in NE differentiation and was downregulated in NEPC cells and tumor specimens. miR-708 targeted Sestrin-3 to inhibit Forkhead Box O1 (FOXO1) phosphorylation, resulting in apoptosis of prostate adenocarcinoma cells and AKT-inactivated NEPC cells, the latter of which was consistent with the progression of tumor xenografts in mice under miR-708 treatment. In silico analysis of PC and NEPC tumor specimens suggested that the polycomb repressive complex subunit Enhancer of zeste homolog 2 (EZH2) was particularly overexpressed in NEPC. Notably, EZH2 bound to the miR-708 promoter and induced its silencing in NEPC. Inhibition of EZH2 prevented NE differentiation of PC cells. EZH2 expression was regulated by both Cyclin Dependent Kinase 1 (CDK1) and Wnt signaling. Silencing transcription factor 4 (TCF4), as a key protein in Wnt signaling, prevented NEPC formation. These results provide a molecular basis for the roles of miR-708 and EZH2 in NE differentiation in PC and highlight a new paradigm in NEPC formation and survival.

Citation:

Shan J, Al-Muftah MA, Al-Kowari MK, et al. Targeting Wnt/EZH2/microRNA-708 signaling pathway inhibits neuroendocrine differentiation in prostate cancer. *Cell Death Discovery.* 2019; 5:139.

Impact Factor: -

Vitamin D Supplementation to Prevent Redevelopment of Basal Cell Carcinoma (BCC): A Phase III Randomized Clinical Trial Protocol

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Abstract

Introduction: Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer and a serious disease leading to increased morbidity and high medical costs worldwide. Despite the high recurrence rate of BCCs, the current standard of care consists of regular skin check-ups, with no know therapy to prevent the recurrence. Vitamin D is a safe, affordable, and easily available supplement used for various diseases. There is evidence suggesting its potential use in preventing BCCs, with studies showing that it inhibits the Hedgehog (HH) signaling pathway, an important stimulator of carcinogenesis and the main pathway in BCC development. The objective of this

study is to determine the effect of oral vitamin D supplementation on the prevention of BCC redevelopment.

Methods: This study is a phase III, multicenter, randomized, placebo-controlled, triple-blinded, superiority trial with two parallel groups on 1:1 allocation of 1746 patients with a previous diagnosis of BCC. The patients will either receive 1000 IU of Vitamin D daily or placebo. During the three-year follow-up period, patients will be undergoing skin check-ups every six months, with laboratorial tests annually. The primary endpoint will be the development of further BCC during 3 years after the initiation of vitamin D supplementation. The statistical analysis will be a time-to-event approach.

Discussion: This is a triple-blinded, randomized, placebo-controlled trial for prevention of a highly prevalent condition. Vitamin D would be a simple solution to prevent the development of further basal cell carcinoma, having tremendous positive effect not only by improving the quality of life of patients, but also by reducing the financial burden on health care systems.

Keywords:

basal cell carcinoma, vitamin D, phase III randomized trial, trial protocol

Citation:

I. Cosgare, Y. Chemale, K. Ahmed, ME. Gunduz, JJ. Rodriguez, MJ. Rodriguez, L.Leonardo, JA. de Oliveira, DS. Schwartz, A. Tamayo, A. Dhawan,BM. Mejia, L. Schonhaut, VO. Olvera, TPA. Fernandes, FJ. Coimbra, VJ. Crestani, FA. Machado, P.Guimarães, G. Constantinescu, Vitamin D Supplementation to Prevent Redevelopment of Basal Cell Carcinoma (BCC): A Phase III Randomized Clinical Trial Protocol. *Principles and Practice of Clinical Research,* 2019, 5(1): 30-35

Impact Factor: -

The Role of the Pharmacist in Decreasing Discharge Medication Discrepancies for Cancer Patients in Qatar: A Prospective Cohort Study

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Abstract

Pharmacy medication reconciliation during admission or at discharge is a crucial step for an error-free patient safety environment. Outpatient Pharmacist (OP) play a lead role in detecting medication-related problems, this urges the need to translate their qualitative values into quantitative measures. Objectives: To investigate the impact of OP intervention during Discharge Reconciliation (DR), in reducing medication errors and discrepancies. In addition, to detecting the most common medication-related problems. Methods: This is a prospective observational study, conducted at the main tertiary cancer hospital (National Centre for Cancer Care and Research) in Qatar. All discharged inpatient that have valid prescriptions were included in the study over a duration of 10 months. A form was generated to be filled by OP in case they encountered a discrepancy or error. The data inputs were collected and categorized into a medication error or discrepancy. A statistical analysis was performed using STATISTICA 11.0 and descriptive statistics. Results: A total of 591 discharged prescriptions with 4293 medications orders included in the study; 278 (47%) prescription required pharmacist intervention. A sum of 190 medication discrepancy and 122 medication errors were detected. The most common medication-related problems were the incomplete orders and restricted medication (34% and 29%, respectively), followed by wrong dose and need of additional drug (18% and 24%, respectively). OP played a significant role in preventing medication errors in a rate of (69/1000 orders) of incomplete orders, (37/1000 orders) of wrong dose and 22/1000 orders of extra doses. Conclusion: The outpatient pharmacist has a significant role towards detecting and reducing medication errors and discrepancies upon patient discharge. However, despite their effective interventions, most of these medications related problems are preventable. We assume that by an improved quality process and awareness, we can create a safe and efficient environment for both patients and healthcare providers

Keywords:

Discharge Medications; Medication Reconciliation; Medication Errors; Pharmacist Interventions; Outpatient Pharmacist

Citation:

T. Abu Hassan, S. Al Yafei, R. M Hussein, S. Nasser, A. Basha, H.Ghazouani and S. Elazzazy*, "The Role of the Pharmacist in Decreasing Discharge Medication Discrepancies for Cancer Patients in Qatar: A Prospective Cohort Study", *ACTA Scientific Cancer Biology* 2019,3.3: 02-09.

Impact Factor: -

Case Reports

ß6-integrin serves as a novel serum tumor marker for colorectal carcinoma

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Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide and the need for novel biomarkers and therapeutic strategies to improve diagnosis and surveillance is obvious. This study aims to identify ß6-ntegrin (ITGB6) as a novel serum tumor marker for diagnosis, prognosis, and surveillance of CRC. ITGB6 serum levels were validated in retro and prospective CRC patient cohorts. ITGB6 serum levels were analyzed by ELISA. Using an initial cohort of 60 CRC patients, we found that ITGB6 is present in the serum of CRC, but not in non CRC control patients. A cut off of ≥2 ng/mL ITGB6 reveals 100% specificity for the presence of metastatic CRC. In an enlarged study cohort of 269 CRC patients, ITGB6 predicted the onset of metastatic disease and was associated with poor prognosis. Those data were confirmed in an

independent, prospective cohort consisting of 40 CRC patients. To investigate whether ITGB6 can also be used for tumor surveillance, serum ITGB6-levels were assessed in 26 CRC patients, pre- and post-surgery, as well as during follow-up visits. After complete tumor resection, ITGB6 serum levels declined completely. During follow-up, a new rise in ITGB6 serum levels indicated tumor recurrence or the onset of new metastasis as confirmed by CT scan. ITGB6 was more accurate for prognosis of advanced CRC and for tumor surveillance as the established marker carcinoembryonic antigen (CEA). Our findings identify ITGB6 as a novel serum marker for diagnosis, prognosis, and surveillance of advanced CRC. This might essentially contribute to an optimized patient care.

Keywords:

Colorectal carcinoma, beta-6-integrin, serum marker, metastasis, tumor surveillance

Citation:

Bengs S, Becker E, Busenhart P, Spalinger MR, Raselli T, Kasper S, Lang S, Atrott K, Mamie C, Vavricka SR, von Boehmer L, Knuth A, Tuomisto A, Mäkinen MJ, Hruz P, Turina M, Rickenbacher A, Petrowsky H, Weber A, Frei P, Halama M, Jenkins G, Sheppard D, Croner RS, Christoph J, Britzen-Laurent N, Naschberger E, Schellerer V, Stürzl M, Fried M, Rogler G, Scharl M. β_6-integrin serves as a novel serum tumor marker for colorectal carcinoma, *International Journal of Cancer*. 2019,145(3):678-685.

Impact Factor: 7.36

A phase I/IIa study of the mRNA-based cancer immunotherapy CV9201 in patients with stage IIIB/IV non-small cell lung cancer.

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Abstract

CV9201 is an RNActive®-based cancer immunotherapy encoding five non-small cell lung cancer-antigens: New York esophageal squamous cell carcinoma-1, melanoma antigen family C1/C2, survivin, and trophoblast glycoprotein. In a phase I/IIa dose-escalation trial, 46 patients with locally advanced (n = 7) or metastatic (n = 39) NSCLC and at least stable disease after first-line treatment received five intradermal CV9201 injections (400-1600 µg of mRNA). The primary objective of the trial was to assess safety. Secondary objectives included assessment of antibody and ex vivo T cell responses against the five antigens, and changes in immune cell populations. All CV9201 dose levels were well-tolerated and the recommended dose for phase IIa was 1600 µg. Most AEs

were mild-to-moderate injection site reactions and flu-like symptoms. Three (7%) patients had grade 3 related AEs. No related grade 4/5 or related serious AEs occurred. In phase IIa, antigen-specific immune responses against ≥ 1 antigen were detected in 63% of evaluable patients after treatment. The frequency of activated IgD+CD38hi B cells increased > twofold in 18/30 (60%) evaluable patients. 9/29 (31%) evaluable patients in phase IIa had stable disease and 20/29 (69%) had progressive disease. Median progression-free and overall survival were 5.0 months (95% CI 1.8-6.3) and 10.8 months (8.1-16.7) from first administration, respectively. Two- and 3-year survival rates were 26.7% and 20.7%, respectively. CV9201 was well-tolerated and immune responses could be detected after treatment supporting further clinical investigation.

Keywords:

Active cancer immunotherapy; CV9201; Clinical trial; Immunomonitoring; Non-small cell lung cancer; mRNA

Citation:

Sebastian M. , Schröder A. , Scheel B. , Hong H. S. , Muth A. , von Boehmer L., Zippelius Al. , Mayer F. , Reck M. , Atanackovic D. , Thomas M. , Schneller F., Stöhlmacher J. , Bernhard H. , Gröschel A. , Lander T. , Probst J. , Strack T. , Wiegand V. , Gnad-Vogt U., . Kallen K., Hoerr I., von der Muelbe F., Fotin-Mleczek M., Knuth A., Koch S. D., A phase I/IIa study of the mRNA-based cancer immunotherapy CV9201 in patients with stage IIIB/IV non-small cell lung cancer, *Immunotherapy*, 2019, 68:799–812

Impact Factor: 4.9

Cerebral schistosomiasis: Case series from Qatar

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Abstract

Schistosomiasis is the third most widespread devastating parasitic disease worldwide and has a high mortality burden. Neuroschistosomiasis is one of the rare and most severe clinical presentations of the disease. It is caused by granuloma formation around eggs that lodge in the central nervous system, with Schistosoma japonicum usually causing most reported cerebral disease. Three unusual presentations of schistosomiasis in Qatar are described herein. The three patients were young males who presented with seizures and tumor-like lesions on brain imaging. The diagnosis was confirmed by biopsy, which showed necrotizing granulomas containing Schistosoma eggs. These cases raise awareness of neuroschistosomiasis as a potential cause of tumor-like brain lesions in migrants and returning travelers from endemic areas.

Keywords:

Granuloma; Neuroschistosomiasis; Schistosoma; Seizure; Tumor-like brain lesion

Citation:

Zaqout A, Abid FB, Murshed K, Al-Bozom I, Al-Rumaihi G, Al Soub H, Al Maslamani M, Al Khal A. Cerebral schistosomiasis: Case series From Qatar. *International Journal of Infectious Diseases*. 2019; 86:167-170:

Impact factor: 3.538

Pancytopenia and Limbic Encephalopathy Complicating Immunotherapy for Clear Cell Endometrial Cancer with Microsatellite Instability-High (MSI-H)

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Abstract

Background: Clear cell carcinoma of the endometrium (CCE) has a tendency to occur in a mismatch repair protein deficient molecular background. Treatment with immunotherapy can predict a favorable response.

Case presentation: We are presenting a 53-year-old female, diagnosed with CCE 17 years ago, who was treated initially with hysterectomy and left salpingo-oophorectomy, who relapsed a few months later, and was then treated with left pelvic mass excision and sigmoidectomy. Recently, the disease recurred as a retroperitoneal lymphadenopathy, which was resected but then relapsed locally, spread to the lungs, and progressed further after three lines of chemotherapy. On pathological review of the tumor, it was found to harbor loss of nuclear expression of MLH-1 and PMS-2. Based on a strong predictor of response to immunotherapy, pembrolizumab was tried. However, within a few days of the single dose of pembrolizumab, immune thrombocytopenia followed by pancytopenia, recurrent seizures, visual hallucination, and cerebellar signs consistent with limbic encephalitis developed, which were not responding to steroid and intravenous immunoglobulin.

Conclusion: We are presenting a case of a CCE with deficient mismatch repair that developed two autoimmune side effects, pancytopenia and limbic encephalitis, within a few days of a single injection of pembrolizumab.

Keywords:

pancytopenia, limbic encephalitis, clear cell endometrial cancer, clear cell carcinoma of the endometrium, microsatellite instability-high, MSI-H, pembrolizumab

Citation:

A. Kanbour, K. Ibrahim Rasul, S. Bujassoum Albader, R. Jawad Al Sulaiman, G. Melikyan, H. Farghaly, Z. Lengyel ,Y. Al Rimawi, D. Soliman, N. Elhadi Omar ,Pancytopenia And Limbic Encephalopathy Complicating Immunotherapy For Clear Cell Endometrial Cancer With Microsatellite Instability-High (MSI-H), *OncoTargets and Therapy*, 2019;12, 9965–9973

Impact Factor: 3.046

Intramural great vessel lymphoma presenting as thrombus in an aortic aneurysm

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Abstract

Intravascular large B-cell lymphoma (IVLBCL) is a subtype of extranodal B-cell lymphoma with growth limited to the lumina of small vessels. Intramural great vessel lymphoma (IMGVL), on the contrary, is extremely rare and there have been only two reported cases of primary B-cell lymphoma that occurred in the lumen of the superior vena cava and one case of primary B-cell lymphoma with intra-aortic growth, diagnosed at autopsy. We present the case of a 72-year-old man who presented with severe abdominal pain and was found to have thrombosed abdominal aortic aneurysm. The retrieved thrombus showed Epstein Barr virus-positive large B cell lymphoma (LBCL). Post-operative Echocardiography, Computerized tomography (CT) and Positron Emission Tomography (PET) scan did not show any residual tumor focus, abnormal mass or thickening, increased FDG uptake or hypermetabolism (Nodal or extranodal). This is the first case of large B cell lymphoma presenting as a thrombus within abdominal aortic aneurysm and third case of intramural great vessel lymphoma.

Keywords:

Lymphoma, Large B cell lymphoma, Aorta, Aneurysm, Intravascular large B cell lymphoma

Citation:

Rashid S., Mohamed S. F., Yassin M., Tbishat L. F., Al-Thani H., Albozom I. Intramural great vessel lymphoma presenting as thrombus in an aortic aneurysm, Human Pathology: Case Reports, 2019, vol 16

Impact factor: 2.740

Fatal renal mucormycosis with *Apophysomyces elegans* in an apparently healthy male

Sameera Rashid [1], Fatma Ben Abid [2], Shafiq Babu [2], Martin Christner [3], **Abdulqadir Alobaidly [4], Abdulla Ali Asad Al Ansari [4], Mohammed Akhtar [1]**

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Abstract

Mucor is an angioinvasive fungus that was reported mainly in immunocompromised patients. It usually presents as rhino-orbital, pulmonary, gastrointestinal, and disseminated disease. Isolated renal mucormycosis is an extremely rare infection in immunocompetent patients and is associated with high fatality rate. Early diagnosis, prompt antifungal treatment, and surgery give the patient the best chance for cure and survival. We describe herein a case of renal zygomycosis caused by *Apophysomyces elegans (A. elegans)* in an immunocompetent host. To the best of our knowledge, this is the first case of renal *A. elegans* to be reported from Qatar and the Middle East.

Keywords:

Fungi; antifungals; immunocompetent; mucormycosis; renal infections

Citation:

Rashid S, Abid F, Babu S, et al. Fatal renal mucormycosis with Apophysomyces elegans in an apparently healthy male, *The Aging Male,* 2019 16:1-4.

Impact factor: 2.5.

Ethical considerations of using a single minor donor for three bone marrow harvests for three HLA-matched siblings with primary immunodeficiency

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Abstract

Allogeneic hematopoietic stem cell transplantation is curative for primary immunodeficiencies. Bone marrow from an unaffected human leukocyte antigen (HLA)-identical sibling donor is the ideal graft source. For minor donors, meaningful consent or assent may not be feasible, and permission from parents or legal guardians is considered acceptable. Adverse events, albeit extremely small, can be associated with bone marrow harvest in pediatric donors. Donor safety concerns potentially increase with multiple bone marrow harvests. Very little is known about multiple bone marrow harvests from pediatric donors. We describe the ethical considerations and clinical decision-making in an unusual clinical situation where three patients with the same primary immunodeficiency were HLA identical to one another and their younger sibling, who underwent bone marrow harvests three times between 1.3 and 4 years of age, resulting in successful transplantation for all three patients. We hope that this experience will provide guidance to providers and families in a similar situation.

Keywords:

chronic granulomatous disease; donor safety; ethical considerations; multiple bone marrow harvests; pediatric marrow donor; primary immunoeficiency

Citation:

Parikh, S., Pentz, R., Haight, A., Adeli, M., Martin, P., Driscoll, T., Page, K., Kurtzberg, J., Prasad, V., Barfield, R. (2019). Ethical considerations of using a single minor donor for three bone marrow harvests for three HLA-matched siblings with primary immunodeficiency. *Pediatric Blood & Cancer*. 2019; 66(4)

Impact Factor: 2.440

Ibrutinib-associated sever skin toxicity: A case of multiple inflamed skin lesions and cellulitis in a 68-year-old male patient with relapsed chronic lymphocytic leukemia - Case report and literature review

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Abstract

Introduction: Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase that is used for a variety of B cell hematological malignancies. Skin and subcutaneous tissue manifestations have been reported and were witnessed in up to 32% of the patients on ibrutinib. The mechanism in which ibrutinib can cause skin toxicities has been thought due to the inhibition of epidermal growth factor; c-Kit and platelet-derived growth factor receptor). Here, we report a case of an elderly chronic lymphocytic leukemia patient who developed multiple inflamed lesions and lower limb cellulitis in 100 days after initiating ibrutinib therapy.

Case report: A 68-year-old male patient with relapsed chronic lymphocytic leukemia was started on ibrutinib 420 mg orally daily following multiple lines of therapy. Three months following ibrutinib, the patient developed multiple hyper pigmented lesions over both forearms then over both thighs; buttocks and lower limbs. The lesions were labeled as ecthyma and cellulitis that started as papules, which progressed to pustules.

Management and outcomes: The patient required admission in which he received prolonged course of antibiotics. Biopsy from the wound showed soft tissue fragment infiltrated by acute and chronic inflammatory cells with necrosis; rare foreign body giant cells and granulation tissue formation; suggestive of abscess. Subsequently, ibrutinib was stopped permanently.

Discussion: This is the first case description of an ibrutinib-associated sever skin toxicity in Qatar. The provided information regarding the clinical descriptions of toxicity profiles in general and skin-based in particular is valuable information for daily clinical practice, especially when selecting the optimum first-line treatment for the patient.

Keywords:

Bruton's tyrosine kinase inhibitor; Ibrutinib; cellulitis; chronic lymphocytic leukemia; skin; toxicity

Citation:

R Ghasoub, A Albattah, S Elazzazy , R Alokka, A Nemir, I Alhijji, R Taha, "Ibrutinib-associated sever skin toxicity: A case of multiple inflamed skin lesions and cellulitis in a 68-year-old male patient with relapsed chronic lymphocytic leukemia – Case report and literature review", *Journal of Oncology Pharmacy Practice* 2019, 26(2):487-491

Impact Factor: 2.42

Repeat liver resection for pure large cell neuroendocrine carcinoma of the gallbladder: a favorable outcome.

Ahmad Abutaka [1], Moamena El-Matbouly [1], Irfan Helmy [2], Walid Elmoghazy [3,4], Ibnouf Sulieman [3], **Mohamed Ben Gashir [5], Madiha Soofi [5]**, Hatem Khalaf [3], **Ahmed Elaffandi [6,7]**

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Abstract

Background: The pure large cell type is a rare variant of primary neuroendocrine carcinoma of the gallbladder. Few reports have mentioned extended survival. Although a multimodal treatment has been described in the treatment of such rare disease, redo liver resection has not yet been mentioned.

Case report: A 67-year-old lady was found to have poorly differentiated, high grade, pure large cell neuroendocrine tumor of the gallbladder after cholecystectomy for gallstones. After the diagnosis, staging workup showed a lesion in segment IVB/V of the liver, and chromogranin was elevated (982 mcg/L). The patient underwent central inferior hepatectomy and wedge excision of a lesion in segment III (discovered intra-operatively), with hilar lymphadenectomy. Three months after the first liver resection, she developed a new liver lesion II/III and underwent left lateral liver resection. The patient remained disease-free for 4 months following the second liver resection but then developed recurrent liver disease and was started on chemotherapy. Further progression led to multi-organ failure and death at 26 months from initial diagnosis.

Conclusion: This is the first reported repeat liver resection in such a rare disease that has led to extended overall survival. We suggest that a group of selected patients with this rare malignancy, and liver-limited disease, may benefit from repeated liver resection.

Keywords:

Cholecystectomy; Gallbladder cancer; Large cell neuroendocrine cancer; Neuroendocrine tumors; Redo liver resection

Citation:

Matbouly M, Helmy I, Elmoghazy W , Sulieman I, Ben Gashir M, Soofi M, Khalaf H, Elaffandi A.Repeat liver resection for pure large cell neuroendocrine carcinoma of the gallbladder: a favorable outcome. *World Journal of Surgical Oncology*. 2019, 20;17(1):126.

Impact Factor: 1.941

Solitary Primary Central Nervous System Lymphoma Mimicking Third Ventricular Colloid Cyst-Case Report and Review of Literature

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Abstract

Background: Primary central nervous system lymphoma is a rare malignant tumor of the central nervous system. It is associated with poor prognosis and accounts for 0.7%-0.9% of all lymphomas and only 0.3%-1.5% of intracranial tumors. Typically, these lesions are in the cerebral white matter near the corpus callosum, the central gray matter, the basal ganglia-thalamus-hypothalamic region, the posterior fossa and the periventricular region. Only 2 cases with pure third ventricular lymphoma have been reported in the literature.

Case description: A 72-year-old female patient known to have type II diabetes mellitus treated with insulin, hypertension, chronic kidney disease, dyslipidemia, and obesity presented with a history of acute confusion and urinary incontinence. No headache was reported on admission, but previously she had intermittent mild headaches and generalized body aches. She had no history of visual symptoms. Her family said she was mildly confused and had memory difficulties that started acutely 2 days before presentation to the hospital. The patient had urgent computed tomography of the brain, which showed a hyperdense lesion in the region of the foramen of Monro. Pre-operative images diagnosed the case as colloid cyst, but post-operative histopathology proved the lesion to be primary CNS lymphoma.

Conclusions: Eleven months after surgery, the patient is fully consciousness and oriented, with no memory issues or neurologic deficit. She is back to her baseline activities. We are reporting this case for the rarity of the disease and the unusual location of it.

Keywords:

Colloid cyst; Endoscopic resection of third ventricular mass; Lymphoma mimicking colloid cyst; PCNSL

Citation:

Haddad R, Alkubaisi A, Al Bozom I, Haider A, Belkhair S. Solitary Primary Central Nervous System Lymphoma Mimicking Third Ventricular Colloid Cyst-Case Report and Review of Literature. *World Neurosurgery,* 2019; 123:286-294.

Impact Factor: 1.723

Mediastinal seminoma presenting as a neck mass falsely diagnosed as anaplastic thyroid carcinoma: A case report.

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Abstract

Germ cell tumors can occur in the mediastinum. They account for about 20% of tumors at this location. The majority are located in the anterior mediastinum and usually occur in young adult males. Extension of mediastinal germ cell tumors into the neck with mass formation is a very rare and unusual event. Herein, we report a case of a 34-year-old male who presented with a progressively enlarging neck mass. Fine Needle Aspiration (FNA) was performed as initial evaluation and showed cellular smears comprising atypical large cells with prominent irregular nucleoli and moderate amount of cytoplasm with lymphocytic infiltrate and some epithelioid granulomas in the background. The mass was misdiagnosed initially on the cytology smears as anaplastic thyroid carcinoma. The subsequent tissue core biopsy showed sheets and nests of atypical cells admixed with ill-defined granulomatous inflammation. By immunohistochemistry, the tumor cells were immunoreactive with SALL4, PLAP and OCT3/4, compatible with malignant germ cell tumor, seminomatous type. It is very rare for patients with primary mediastinal seminoma to present initially with a neck mass. Fine Needle Aspiration (FNA) of this "neck mass" can lead to misinterpretation of findings due to similarities in cytological features between malignant germ cell tumors and other undifferentiated malignant neoplasms and the diagnosis, therefore, can be very challenging.

Keywords

anaplastic thyroid carcinoma; fine needle aspiration; mediastinal seminoma

Citation:

Murshed K, Al-Bozom I, Vattoth S, Akhtar M. Mediastinal seminoma presenting as a neck mass falsely diagnosed as anaplastic thyroid carcinoma: A case report. *Diagnostic Cytopathology*. 2019; 47:334–336.

Impact factor: 1.402

Hemolytic Anemia After Relapse of Chronic Myeloid Leukemia: A Case Report

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Abstract

Autoimmune hemolytic anemia is one of the differential diagnoses for anemia in patients with lymphoproliferative neoplasia, such as chronic lymphocytic leukemia, who experience sudden drop in hemoglobin. The association between autoimmune hemolytic anemia and chronic myeloid leukemia on the contrary is unusual. Here we present a patient with a background of chronic myeloid leukemia treated previously with Tyrosine Kinase Inhibitors, then developed autoimmune hemolysis simultaneously with chronic myeloid leukemia relapse. Hemolysis was treated with steroids with good response.

Keywords:

chronic myeloid leukemia (CML), autoimmune hemolytic anemia (AIHA)

Citation:

Hamamyh, T., Yassin M. A. "Autoimmune Hemolytic Anemia After Relapse of Chronic Myeloid Leukemia: A Case Report." *Clinical medicine insights. Blood disorders*, 2019; vol. 12

Impact Factor: 0.95

Thoracic Spinal Intramedullary Arachnoid Cyst Presented with Myelopathy with Marked Postoperative Improvement: A Case Report and Review of Literature

Ahmed Shaaban, Amrou Abdelrahman, Raed Abu Jarir, Issam Al-Bozom[1], Ali Raza

Departments of Neurosurgery and [1]Pathology, Hamad General Hospital, Doha, Qatar

Abstract:

Intramedullary spinal cord arachnoid cysts are rare. So, we present an interesting case of adult male presented with myelopathic symptoms and signs. Further investigations revealed a finding of thoracic intramedullary cystic lesion found postoperatively to be an arachnoid cyst. Patient improved remarkably postoperative and during follow up period.

Keywords:

Arachnoid cyst, intramedullary, spinal cord

Citation:

Shaaban A, Abdelrahman A, Jarir RA, Al-Bozom I, Raza A. Thoracic spinal intramedullary arachnoid cyst presented with myelopathy with marked postoperative improvement: A case report and review of literature. *Asian Journal of Neurosurgery*, 2019;14:981-4.

Impact Factor: 0.905

Spontaneous iliopsoas hematoma in a transfusion dependent β-thalassemia patient with hypersplenism: a case report

Aishwariya Padmakumari[1], Mohammed Talat[2], Ashraf Soliman[3], Vincenzo De Sanctis[4], **Abdulqadir Nashwan[5], Mohamed A Yassin[6]**

[1] Department of Medical Education Hamad Medical Corporation (HMC), Doha, Qatar; [2] Department of Radiology, Hamad Medical Corporation (HMC), Doha, Qatar; [3] Department of Pediatrics, University of Alexandria, Alexandria, Egypt; [4] Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; **[5] Nurse Research Scientist, Cancer Clinical Trials Unit, NCCCR, Hamad Medical Corporation (HMC), Doha, Qatar; [6] Hematology Section, National Center for Cancer Care and Research, Hamad Medical Corporation, (HMC), Doha, Qatar**

Abstract

Summary. A 27-year-old married man with transfusion dependent β-thalassemia (TDT) complaining low back pain due to a spontaneous iliopsoas hematoma is reported. A magnetic resonance imaging (MRI) confirmed the diagnosis. The patient was managed conservatively. The mechanism of spontaneous iliopsoas hematoma was unclear, although tearing of muscle fibers, unrecognized minor trauma, low platelet count, secondary to hypersplenism, and severe liver iron overload, associated to abnormalities of clotting factors synthesis, were the suspected etiologies. He showed a good response to treatment and was discharged home 11 days later. A new MRI performed 7 months later, showed a complete resolution of hematoma. Although iliopsoas haematoma is an uncommon complication in patients with akik, it should be considered in the differential diagnosis of a patient with back pain.

Key words:

iliopsoas hematoma, transfusion dependent β-thalassemia, diagnosis, treatment. Hypersplenism

Citation:

admakumari A., Talat M., Soliman A., De Sanctis V., Nashwan A., Yassin M. A. Citation: Spontaneous iliopsoas hematoma in a trasfusion dependent β-thalassemia patient with hypersplenism: a case report, *Acta Biomed* 2019; Vol. 90, N. 1: 107-111

Impact Factor: 0.77

Imatinib-Induced Tremor in a Patient with Chronic Myeloid Leukemia in Chronic Phase

Khaldun Obeidat [1], Arwa Alsaud [1], Amr Ashour [1], Bahjat Azrieh [2], Mohammad Abu-Tineh [1], Shehab Fareed Mohamed [2], Mohamed A Yassin [2]

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by three phases: chronic, accelerated, and blast phase. However; first- and second-generation tyrosine kinase inhibitors are used for the treatment of CML with common and uncommon adverse events. Here, we report a 24-year-old male with CML in chronic phase started on imatinib as upfront medication who developed tremor and recovered spontaneously after 3 years.

Keywords:

Chronic myeloid leukemia, Imatinib, Side effects , Tremor, Tyrosine kinases

Citation:

Obeidat K., Alsaud A., Ashour A., Azrieh B., Abu-Tineh M., Mohamed S.F., Yassin M.A.Imatinib-Induced Tremor in a Patient with Chronic Myeloid Leukemia in Chronic Phase, *Case Reports in Oncology* 2019, Vol.12, No. 3

Impact Factor: 0.71

Paroxysmal Nocturnal Hemoglobinuria with Glucose-6-Phosphate Dehydrogenase Deficiency: A Case Report and Review of the Literature

Mahmoud S. Eisa,[1] Shehab F. Mohamed,[2] Firyal Ibrahim,[2] Khalid Shariff,[1] Nagham Sadik,[1] Abdulqadir Nashwan,[2] and Mohamed A. Yassin[2]

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Abstract

In this study, we are describing a female patient with paroxysmal nocturnal hemoglobinuria (PNH) and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Both diseases are known to cause hemolytic anemia that mediates the hemolysis of RBCs through several mechanisms. In PNH the hemolysis is mediated through complement activation and oxidative stress. G6PD enzyme is crucial in preventing damage to cellular structures caused by oxygen-free radicles. In G6PD deficiency the hemolysis is mediated through the oxidative stress created by oxygen-free radicles. Since both diseases mediate hemolysis through the oxidative stress, we hypothesize that both conditions have facilitated an effect on each other and this will reflect on the response to treatment, and this response to treatment could vary based on whether the two mutations occurred in the same gene or in two different X chromosomes. Having diagnosed PNH, the management is very expensive and not all the patients can afford it, especially our patient who is a maid by occupation. So, the real challenge in our case is to monitor her in subsequent visits and to plan the treatment keeping in mind her financial status.

Keywords:

Paroxysmal nocturnal hemoglobinuria, Eculizumab, G6PD

Citation:

Eisa, M. S., Mohamed, S., Ibrahim, F., Shariff, K., Sadik, N., Nashwan, A., Yassin, M.). Paroxysmal Nocturnal Hemoglobinuria with Glucose-6-Phosphate Dehydrogenase Deficiency: A Case Report and Review of the Literature. *Case Reports in Oncology*. 2019; 12. 838-844.

Impact Factor: 0.71

Concomitant BRAF Mutation in Hairy Cell Leukemia and Papillary Thyroid Cancer: Case Report

Shehab F Mohamed [1], Feryal Helmi [2], Susanna El-Akiki [2], Halima El Omri [1], Abdulqadir Nashwan [1], Mohamed A Yassin [1]

[1]Hematology Department, National Center for Cancer Research (NCCCR), Hamad Medical Corporation, Doha, Qatar. [2]Department of Laboratory Medicine and Pathology, Hamad Medical Corporation, Doha, Qatar.

Abstract

Hairy cell leukemia (HCL) is rare type of leukemia. This neoplasm is well-known to present with pancytopenia and splenomegaly. HCL is associated with BRAF mutation in 100% of cases. It is also associated with hematological and oncological malignancies such as melanoma and papillary thyroid cancer. Although the association of both cancers (HCL and papillary thyroid cancer) with BRAF mutation is well established in the literature, as far as we know it has not been reported before in the same patient. Here we report 48-year-old male diagnosed with HCL and papillary thyroid cancer and who is BRAF positive in both diagnostic tissues.

Keywords:

BRAF; Hairy cell leukemia; Papillary thyroid cancer

Citation:

Mohamed S, F, Helmi F, El-Akiki S, El Omri H, Nashwan A, Yassin M, A: Concomitant BRAF Mutation in Hairy Cell Leukemia and Papillary Thyroid Cancer: Case Report. *Case Reports Oncology* 2019; 12:922-927.

Impact factor: 0.71

Sore throat turned to be a bronchogenic carcinoma with superior vena cava syndrome.

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Abstract

Superior vena cava (SVC) syndrome is a group of symptoms caused by complete or partial obstruction of the flow of blood through the SVC. The obstruction is, in most cases, caused by the formation of thrombus or infiltration of a tumour through the vessel wall. The result is venous congestion that creates a clinical situation relating to increase in the venous pressure in the upper part of the body. Symptoms commonly associated with vena cava syndrome include cough, dyspnoea, swelling of the neck, face and the upper extremities and dilation of the chest vein collaterals. In this paper, we examine the case of a 50-year-old man who presented to the emergency department with 'sore throat' which can be easily misdiagnosed as a case of uncomplicated acute pharyngitis. It was a real challenge to diagnose our patient as SVC syndrome caused by bronchogenic carcinoma.

Keywords:

cardiovascular medicine; emergency medicine; lung cancer (oncology); respiratory medicine

Citation:

Elmoheen A, Eltawagny M, Elmesery A, Bashir K. Sore throat turned to be a bronchogenic carcinoma with superior vena cava syndrome. *BMJ Case Reports*. 2019;12(12).

Impact factor: 0.44

An Unusual Cause of a Pancreatic Mass: Pancreatic Tuberculosis

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Abstract

Isolated pancreatic tuberculosis (TB) is an exceedingly rare disease, even in countries with a high burden of TB. We report the case of a 40-year-old gentleman who presented with a twoweek history of fever and abdominal pain. Computed tomography of the abdomen showed a large heterogeneous mass arising from the pancreas with peri-pancreatic lymphadenopathy, infiltration of the stomach, and encasement of the celiac vessels-highly suggestive of pancreatic malignancy. Oesophagogastroduodenoscopy with endoscopic ultrasonography was performed, which showed a necrotic area in the body of pancreas. Fine needle aspiration from the necrotic area was positive for Mycobacterium tuberculosis by polymerase chain reaction (PCR) and culture methods. This case demonstrates an unusual presentation of TB with predominant involvement of the pancreas in the absence of pulmonary or systemic involvement. Clinicians need to be aware of this unique presentation of tuberculosis in order to avoid misdiagnosis and institute timely treatment.

Keyword:

Internal Medicine, Gastroenterology, Infectious Disease Keywords: acid fast bacilli, endoscopic ultrasound, tuberculosis, mycobacterium tuberculosis, pancreatic tuberculosis

Citation:

Rehman A, Maliyakkal A, Farfar K L, et al. An Unusual Cause of a Pancreatic Mass: Pancreatic Tuberculosis. *Cureus* 2019, 11(5): e4732.

Impact Factor: -

Subcutaneous Nematode Mimicking Soft Tissue Neoplasm: A Case Report with Review of Literature

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[1]Department of Lab medicine & Pathology, Histopathology section, Hamad Medical Corporation, Doha, Qatar

Abstract:

Parasitic infections can involve various organs of the human body; one the most common sites is the gastrointestinal tract. Their identification as isolated organ involvement in the soft tissues is unusual and under diagnosed event. Herein, we report a case of a 15-year-old Indian male patient who presented with soft tissue swelling in his right arm. MRI imaging revealed an oval-shaped mass lesion measuring 2 cm in diameter with intense post-contrast enhancement and non-enhancing center. Soft tissue neoplasm was suspected, and direct surgical wide excision of the mass was performed. Unexpectedly, histopathologic examination revealed Nematode worms with exuberant tissue response causing this mass lesion.

Parasitic infections should be considered in the differential diagnosis of soft tissue lesions, especially in endemic populations or when there is a history of travel or immigration from an endemic region. If such lesions are misdiagnosed as a neoplastic process, this may lead to unnecessary overtreatment for a disease meant be cured by simple surgical excision and antiparasitic medications.

Keywords:

Parasite; Nematode infection; Soft tissue neoplasm

Citation:

Murshed K, Sibira R, Adham A., Subcutaneous Nematode Mimicking Soft Tissue Neoplasm: A Case Report with Review of Literature. *Journal of Emergency, Critical Care, Diagnostic Managements*, 2019, 2(1): 1-3.

Impact factor: -

Multilocular cystic renal neoplasm of low malignant potential extending into the perinephric adipose tissue

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Department of Lab Medicine and Pathology – Histopathology section, Hamad Medical Corporation, Doha, State of Qatar

Abstract

Multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) is a rare variant and a distinct subtype of clear cell renal cell tumors that has a favorable outcome. Most of the cases present with a low pathologic stage at diagnosis (T1 or T2). It is unusual for this tumor to extend into the perinephric adipose tissue, renal sinus fat or renal vein. There are very few cases reported in the literature to have a higher pathologic stage (pT3 and above) at diagnosis. Here, we report a case of MCRNLMP with unusual rare finding in which the tumor has extended into the surrounding perinephric adipose tissue.

Keywords:

Multilocular cystic renal neoplasm of low malignant potential, Multilocular cystic renal cell carcinoma, Perinephric fat invasion

Citation:

Murshed KA, Akhtar M, Ben-Gashir M. Multilocular cystic renal neoplasm of low malignant potential extending into the perinephric adipose tissue. *Human Pathology: Case Reports*. 2019; 17, 200305.

Impact Factor: -

Hairy Cell Leukemia Presenting as Presternal Soft Tissue Mass

Khaled Murshed Abdelfattah[1], Afraa Fadul[2], Mohamed Yassin[2], Feryal Hilmi[3], Ahmed Mounir Elsayed[4], Issam Al-Bozom[1]

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Abstract

Hairy cell leukemia (HCL) is an uncommon chronic lymphoproliferative disorder. Initial presentation frequently includes symptoms related to peripheral blood cytopenias. It can sometimes have atypical manifestations and can present at unusual sites. We report an unusual presentation of HCL as a presternal soft tissue mass in a 45-year-old man. His peripheral blood counts showed pancytopenia. There were no palpable lymph nodes or hepatosplenomegaly. CT-scan revealed a middle mediastinal mass with extension into the presternal soft tissue. Tissue core biopsy was taken and histopathologic findings confirmed the diagnosis of HCL. To our knowledge, this is the second reported case of HCL presenting as a presternal soft tissue mass. Although rare, HCL should be considered in the differential diagnosis of tumors involving extramedullary/extranodal sites including the soft tissue and bone, so the patient can get the utmost benefit for early diagnosis of a treatment responsive disease.

Citation:

Murshed KA, Fadul A, Yassin MA, Hilmi F, Elsayed AM, Al-Bozom I. Hairy Cell Leukemia Presenting as Presternal Soft Tissue Mass: A Case Report With Review of Literature. *American Journal of Surgical Pathology: Reviews & Reports.* 2019; 24 (6), 281-282.

Impact factor: -

Cisplatin-Gemcitabine Related Cardiomyopathy in Non-Small Cell Lung Cancer NSCLC Patient: A Case Study

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[1]Department of Pharmacy, National Center of Cancer Care and Research, Doha, Qatar [2] Department of Medical Oncology, National Center of Cancer Care and Research, Doha, Qatar

Abstract

Gemcitabine is a pyrimidine analog and cisplatin is a platinum agent, they are usually combined to form a chemotherapeutic doublet used to treat different types of oncological cancers, including non-small cell lung cancer (NSCLC). Although these agents are not known to cause such events, few cases related to possible cardiotoxicity side effects have been reported; including angina, chronic heart failure, arrhythmias, and cardiac ischemia. A 52-year-old African male presented with Stage IV lung adenocarcinoma metastatic to the bone, pleura and lymph node, EGFR wild type. Patient has a history of hypertension, diabetes, and atrial fibrillation and on rate control medications. He was treated initially with cisplatin-gemcitabine, after which he developed cardiomyopathy. This was proven by a two-dimensional echocardiography with an ejection fraction dropping from 65% to 35%. In our perspective, cardiomyopathy could be related to cisplatin-gemcitabine, which is a rare but potential risk factor for developing cardiomyopathy especially if the patient has pre-existing comorbidities that may potentiate toxicity. An instant discontinuation with close monitoring is needed. Furthermore, we suggest considering other options of chemotherapy for patients if they develop cardiac adverse events.

Keywords:

Cisplatin-Gemcitabine; Adverse Drug Reactions; Anthracyclines; Cardiomyopathy; Pharmaco-Epidemiology; Platinum Chemotherapy; Cardiotoxicity

Citation:

Dawoud RA, Hind Elmalik, AL-Azzazy S (2018) Cisplatin-Gemcitabine Related Cardiomyopathy in Non-Small Cell Lung Cancer NSCLC Patient: A Case Study. *Journal of Case Reports and Studies* ,2019; 6(4): 406

Impact Factor: -

Highly Aggressive CD4-Positive Mast Cell Leukemia (Leukemic Variant) Associated with Isolated Trisomy 19 and Hemophagocytosis by Neoplastic Mast Cells: A Case Report with Challenging Experience and Review

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[1]Department of Laboratory Medicine and Pathology, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar [2]Clinical Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt [3]Clinical Pathology and Laboratory Medicine, Weill-Cornell Medicine, Doha, Qatar **[4]Department of Hematology and Medical Oncology, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar**

Abstract

Background. Mast cell leukemia is a unique disease among hematopoietic neoplasms, being one of the rarest leukemia subtypes. In addition, its prompt diagnosis is usually challenging. This is due to its heterogeneity in clinical presentations and cytomorphological and immunophenotypical features together with potential associations with other hematologic neoplasms which can complicate the condition and delay accurate diagnosis. To the best of our knowledge, this is the first case report of CD4-positive mast cell leukemia. Case Presentation. A 39-year-old male presented with acute onset of fever, abdominal pain, and generalized body aches of two-week duration. Peripheral blood smear showed circulating blasts (13%) with coarsely basophilic granulation. Bone marrow (BM) aspirate showed extensive infiltration with immature mast cells of blast-like morphology with trilineage dysplasia and evident hemophagocytic activity exhibited by histiocytes and neoplastic mast cells. BM biopsy was diffusely infiltrated with many atypical mast cells positive for CD45, CD117, mast cell tryptase, CD25, and CD4 with partial positivity for CD7 and CD30. Cytogenetics showed an abnormal karyotype: 47, XY, +1947, XY, +19[13]/46, XY[9]. Molecular analysis revealed a KIT D816V mutation consistent with a diagnosis of systemic mastocytosis, mast cell leukemia. Conclusion. The expression of T-cell associated markers by abnormal mast cells is well documented; however, CD4 and CD7 expression have not previously been described in association with mast cell leukemia. Coexpression of CD2, CD4, CD7, and CD30 by the mast cells particularly in skin lesions may provoke misinterpretation as a cutaneous T-cell neoplasm. To the best of our knowledge, this is the first report of CD4-positive mast cell leukemia. Moreover, hemophagocytic mast cell leukemia is a very rare morphologic variant, and possible correlation between this finding and expression of CD4 by neoplastic mast cells is a topic for further investigation.

Citation:

Soliman, D., Al-Sabbagh, A., Ibrahim, F., Gameil, A., Yassin, M., Omri, H. Highly Aggressive CD4-Positive Mast Cell Leukemia (Leukemic Variant) Associated with Isolated Trisomy 19 and Hemophagocytosis by Neoplastic Mast Cells: A Case Report with Challenging Experience and Review. *Case Reports in Hematology*, 2019; 1-9.

Impact factor:

Heterotopic Gastric Mucosa Presenting as Lower Gastrointestinal Bleeding: An Unusual Case Report

Syed Muhammad Ali [1], Ayman Abdelhafiz Ahmed [2], Leena Amin Hussain Saaid [1], Gihan Mustafa Kamal Mohamed [1], Amjad Ali Shah [1], Mohannad Al-Tarakji [1], Zia Aftab [1], Inamulla [1], Sameera Rashid [3]

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Abstract

Heterotopic gastric mucosa (HGM) is gastric mucosal tissue outside the stomach. It can be discovered anywhere throughout the gastrointestinal tract and is mostly asymptomatic. HGM, although rare beyond the ligament of Treitz, should be included in the differential diagnosis in a young patient with a polyp causing obstructive symptoms or bleeding. Very few cases are published in literature. We describe a case of young male who presented with an episode of large amount of melena, from a bleeding jejunal lesion, diagnosed by endoscopy. Laparotomy and wedge resection of the jejunal lesion was done, and histopathology showed gastric heterotopia in a small jejunal diverticulum.

Citation:

Syed Muhammad Ali, Ayman Abdelhafiz Ahmed, Leena Amin Hussain Saaid, et al., "Heterotopic Gastric Mucosa Presenting as Lower Gastrointestinal Bleeding: An Unusual Case Report," *Case Reports in Surgery* 2019., vol. 2019

Impact factor: -

Cystic poorly differentiated squamous cell carcinoma of the scalp, a rare scalp tumor: Case report and literature review.

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Abstract

Introduction: Cutaneous cystic lesions have broad differentials ranging from common benign entity to rare malignant lesions. Clinical evaluation of the lesion is the key to differentiation, as some rare malignant entities may simulate benign lesions. A high index of suspicion should be maintained for any aggressive behavior, which may require more thorough evaluation, including histopathology and radiographic imaging studies. We report a rare case of cystic poorly differentiated squamous cell carcinoma (CPDSCC) of the scalp.

Case presentation: We report a case of a 37-year-old Filipino expatriate male who presented with a scalp swelling which had been gradually increasing in size for four months and was operated upon with a working diagnosis of sebaceous cyst. On post-op excisional biopsy, it turned out to be poorly differentiated cystic squamous cell carcinoma of the scalp. On further workup, no metastasis or other primary was found. Complete re-excision of the lesion with no evidence of residual tumor was achieved. Long-term follow-up was lost, as the patient left for his native country.

Conclusion: Though cystic cutaneous lesions are very commonly encountered in clinical practice, high suspicion for malignancy should be maintained if the lesion shows any aggressive behavior. Prompt investigation should be done before surgery to determine the nature of the disease and the most effective management for the patient. Poorly differentiated cystic squamous cell carcinoma should also be considered in the differential diagnosis of cystic cutaneous lesions show aggressive behavior.

Keywords:

Cystic; Dermoid; Epidermoid cyst; Malignant; Metastatic; Squamous cell carcinoma; Trichilemmal carcinoma

Citation:

Shah A, Akram J, Abdelaal A, Alateeq L, Ben-Gashir M, Hammouda A , Cystic poorly differentiated squamous cell carcinoma of the scalp, a rare scalp tumor: Case report and literature review. *International Journal of Surgical Case Reports*. 2019; 60:21-24.

Impact Factor: -

Olfactory Groove Meningioma

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Abstract

The most frequent primary brain tumours in adults are gliomas and primary CNS lymphomas. Meningioma represents about 30 percent of them. This tumor is usually slow-growing tumor that arises from the meninges, the membranous layers surrounding the brain and spinal cord. Symptoms depend on the location and occur as a result of the mass effect on adjacent tissue. One of these locations is subfrontal olfactory groove. These kinds of meningiomas arise from the meningeal coverings of the cribriform plate or the front osphenoidal suture. Olfactory Groove Meningiomas (OGMs) are typically non-cancerous and account about 10 percent of all meningiomas, according to the American Brain Tumor Association (ABTA). Olfactory groove meningiomas develop insidiously and their diagnosis is commonly made late, when tumors are large. Their treatment is therefore mostly surgical. In this report, we specifically focus on the clinical presentation as well as the radiologic characteristics of this disease based on a case that has been admitted at Zawia Teaching Hospital, Libya. Furthermore, we would discuss some newly recommended surgical approaches. We present this unusual case that has been diagnosed successfully by MRI.

Keywords:

Brain tumor; Meningioma; Olfactory groove; Subfrontal extra axial mass

Citation:

Hussein ML, Mira RR, Mathew V. Olfactory Groove Meningioma. *Indian Journal of Applied Radiology*. 2019;5(1): 131.

Impact Factor: -

Reviews

Extracellular vesicles-mediated intercellular communication: roles in the tumor microenvironment and anti-cancer drug resistance

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Abstract

The tumor microenvironment represents a complex network, in which tumor cells not only communicate with each other but also with stromal and immune cells. Current research has demonstrated the vital role of the tumor microenvironment in supporting tumor phenotype via a sophisticated system of intercellular communication through direct cell-to-cell contact or by classical paracrine signaling loops of cytokines or growth factors. Recently, extracellular vesicles have emerged as an important mechanism of cellular interchange of bioactive molecules. Extracellular vesicles isolated from tumor and stromal cells have been implicated in various steps of tumor progression, such as proliferation, angiogenesis, metastasis, and drug resistance. Inhibition of extracellular vesicles secretion, and thus of the transfer of oncogenic molecules, holds promise for preventing tumor growth and drug resistance. This review focuses on the role of extracellular vesicles in modulating the tumor microenvironment by addressing different aspects of the bidirectional interactions among tumor and tumor-associated cells. The contribution of extracellular vesicles to drug resistance will also be discussed as well as therapeutic strategies targeting extracellular vesicles production for the treatment of cancer.

Keywords:

Drug resistance; Extracellular vesicles; Metastasis; Stroma; Tumor microenvironment

Citation:

Maacha S, Bhat AA, Jimenez L, Raza A, Haris M, Uddin S, Grivel JC. Extracellular vesicles-mediated intercellular communication: Roles in the tumor microenvironment and anti-cancer drug resistance. *Molecular Cancer*. 2019 30;18(1):55

Impact Factor: 10.679

The Role of Extracellular Vesicles as Modulators of the Tumor Microenvironment, Metastasis and Drug Resistance in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is one of the most common cancers worldwide, with high morbidity and mortality rates. A number of factors including modulation of the tumor microenvironment, high metastatic capability, and resistance to treatment have been associated with CRC disease progression. Recent studies have documented that tumor-derived extracellular vesicles (EVs) play a significant role in intercellular communication in CRC via transfer of cargo lipids, proteins, DNA and RNAs to the recipient tumor cells. This transfer influences a number of immune-related pathways leading to activation/differentiation/expression of immune cells and modulation of the tumor microenvironment that plays a significant role in CRC progression, metastasis, and drug resistance. Furthermore, tumor-derived EVs are secreted in large amounts in biological fluids of CRC patients and as such the expression analysis of EV cargoes have been associated with prognosis or response to therapy and may be a source of therapeutic targets. This review aims to provide a comprehensive insight into the role of EVs in the modulation of the tumor microenvironment and its effects on CRC progression, metastasis, and drug resistance. On the other hand, the potential role of CRC derived EVs as a source of biomarkers of response and therapeutic targets will be discussed in detail to understand the dynamic role of EVs in CRC diagnosis, treatment, and management.

Keywords:

biomarker; colorectal cancer; drug resistance; extracellular vesicles; metastasis; miRNA; tumor microenvironment

Citation:

Siveen, K.S.; Raza, A.; Ahmed, E.I.; Khan, A.Q.; Prabhu, K.S.; Kuttikrishnan, S.; Mateo, J.M.; Zayed, H.; Rasul, K.; Azizi, F.; Dermime, S.; Steinhoff, M.; Uddin, S. The Role of Extracellular Vesicles as Modulators of the Tumor Microenvironment, Metastasis and Drug Resistance in Colorectal Cancer. *Cancers* 2019, 11, ;11(6). pii: E746.

Impact Factor: 6.1

Virus-like particles for vaccination against cancer

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Abstract

Active immunotherapy of cancer aims to treat the disease by inducing effective cellular and humoral immune responses. Virus-like particle-based vaccines have evolved dramatically over the last few decades, greatly reducing morbidity and mortality of several infectious diseases and expectedly preventing cervical cancer caused by human papilloma virus. In contrast to these broad successes of disease prevention, therapeutic cancer vaccines remain to demonstrate clinical benefit. Yet, several preclinical and clinical trials have revealed promising results and are paving the way for medical breakthroughs. This study reviews and discusses the recent preclinical development and clinical trials in this field. This article is categorized under: Biology-Inspired Nanomaterials > Protein and Virus-Based Structures Nanotechnology Approaches to Biology > Nanoscale Systems in Biology

Keywords:

cancer, vaccine, virus like particles

Citation:

Mohsen MO, Speiser DE, Knuth A, Bachmann MF. Virus-like particles for vaccination against cancer. *WIREs Nanomedicine and Nanobiotechnology*. 2019, 27: e1579.

Impact Factor: 6.14

Role of miRNA-Regulated Cancer Stem Cells in the Pathogenesis of Human Malignancies

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Abstract

Recent biomedical discoveries have revolutionized the concept and understanding of carcinogenesis, a complex and multistep phenomenon which involves accretion of genetic, epigenetic, biochemical, and histological changes, with special reference to MicroRNAs (miRNAs) and cancer stem cells (CSCs). miRNAs are small noncoding molecules known to regulate expression of more than 60% of the human genes, and their aberrant expression has been associated with the pathogenesis of human cancers and the regulation of stemness features of CSCs. CSCs are the small population of cells present in human malignancies well-known for cancer resistance, relapse, tumorigenesis, and poor clinical outcome which compels the development of novel and effective therapeutic protocols for better clinical outcome. Interestingly, the role of miRNAs in maintaining and regulating the functioning of CSCs through targeting various oncogenic signaling pathways, such as Notch, wingless (WNT)/ß-Catenin, janus kinases/ signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol 3-kinase/ protein kinase B (PI3/AKT), and nuclear factor kappa-light-chain-enhancer of activated B (NF-kB), is critical and poses a huge challenge to cancer treatment. Based on recent findings, here, we have documented the regulatory action or the underlying mechanisms of how miRNAs affect the signaling pathways attributed to stemness features of CSCs, such as self-renewal, differentiation, epithelial to mesenchymal transition (EMT), metastasis, resistance and recurrence etc., associated with the pathogenesis of various types of human malignancies including colorectal cancer, lung cancer, breast cancer, head and neck cancer, prostate cancer, liver cancer, etc. We also shed light on the fact that the targeted attenuation of deregulated functioning of miRNA related to stemness in human carcinogenesis could be a viable approach for cancer treatment.

Keywords:

cancer; cancer stem cells; human malignancies; miRNA; signaling

Citation:

Khan AQ, Ahmed EI, Elareer NR, Junejo K, Steinhoff M, Uddin S. Role of miRNA-Regulated Cancer Stem Cells in the Pathogenesis of Human Malignancies. *Cells.* 2019, 5;8(8):840.

Impact Factor: 5.565

Renal Cell Carcinoma (PRCC): An Update

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Abstract

Papillary renal cell carcinoma (PRCC) is the second most common type of renal carcinoma following clear cell renal cell carcinoma. Papillary renal cell carcinoma is usually divided histologically into 2 types namely, type 1 and type 2. This classification, however, is unsatisfactory as many of papillary carcinoma are unclassifiable by the existing criteria. In recent years there has been a remarkable progress in our understanding of the molecular basis of PRCC. These studies have revealed that type 2 PRCCs represent a heterogenous group which may be subdivided into additional subtypes based on the genetic and molecular make up of these tumors and reflecting different clinical course and prognosis. Some of the molecular features such a hypermethylation of CPG islands in the promotor regions of genes and over expression of the antioxidant pathways within tumor cells have been recognized as markers of poor prognosis. Targeted therapies for papillary carcinoma in the past have been unsuccessful because of lack of clear understanding of the molecular basis of these tumors. It is hoped that recent progress in our understanding of the pathogenesis of various subtypes of PRCC, effective targeted therapies will eventually emerge in due course.

Keyword:

c-Met; familial; next generation sequencing; papillary; renal carcinoma; sporadic; type 1; type 2

Citation:

Akhtar M., Al-Bozom I., Al Hussain T.,Papillary Renal Cell Carcinoma (PRCC): An Update. *Advances in Anatomic Pathology*, 2019 Volume 26, Number 2, pp. 124-132

Impact factor: 3.53

Urothelial Carcinoma in Situ (CIS): New Insights

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Abstract

Urothelial carcinoma in situ (CIS) is a high-grade noninvasive malignancy with a high tendency of progression. Although it is typically grouped with other nonmuscle invasive bladder cancers, its higher grade and aggressiveness make it a unique clinical entity. Urothelial CIS is histologically characterized by replacement of the urothelium by cells which fulfill the morphologic criteria of malignancy including nuclear pleomorphism, hyperchromasia, prominent nucleoli, and increased numbers of normal and abnormal mitoses. Urothelial CIS may be categorized as primary when it is not associated with any past or present urothelial carcinoma. It is termed as secondary when there is concomitant or previous urothelial carcinoma in the patient. In recent years detailed molecular studies have provided valuable data for intrinsic molecular subclassification of urothelial carcinoma into 2 broad categories namely luminal and basal types with significant implications for prognosis and therapy. Similar studies on urothelial CIS are limited but have provided crucial insight into the molecular basis of CIS. These studies have revealed that urothelial CIS may also be divided into luminal and basal subtypes, but luminal subtype is much more common. It has also been shown that in many cases, luminal type of urothelial CIS may undergo a class switch to basal type during progression to an invasive carcinoma. Additional studies may be required to confirm and further elaborate these findings.

Citation:

Akhtar M, Al Bozom I, Ben Gashir, Rashid S. Urothelial Carcinoma in Situ (CIS): New Insights. *Advances in Anatomic Pathology* 2019 - Volume 26 - Issue 5 - p 313–319

Impact factor: 3.530

Paget's "Seed and Soil" Theory of Cancer Metastasis: An Idea Whose Time has Come

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Abstract

The concept that the pattern of metastatic spread of cancer is not random and that cancer cells exhibit preferences when metastasizing to organs, dates back to 1889 when Steven Paget published his "seed and soil" hypothesis. He proposed that the spread of tumor cells is governed by interaction and cooperation between the cancer cells (seed) and the host organ (soil). Extensive studies during the last several decades have provided a better understanding of the process of metastatic spread of cancer and several stages such as intravasation, extravasation, tumor latency, and development of micrometastasis and macrometastasis have been defined. Furthermore, recent studies have shown that the target organs may be prepared for metastatic deposits by the development of premetastatic niches. This specialized microenvironment is involved in promoting tumor cell homing, colonization, and subsequent growth at the target organ. The premetastatic niche consists of accumulation of aberrant immune cells and extracellular matrix proteins in target organs. The primary tumor plays a key role in the development of premetastatic niches by producing tumor-derived soluble factors which mobilize bone marrow-derived hematopoietic cells to the premetastatic niche. Exosomes-derived from the primary tumor also contribute to cancer-favorable microenvironment in the premetastatic niches. These changes prime the initially healthy organ microenvironment and render it amenable for subsequent metastatic cell colonization.

Key words:

bonemarrow; exosomes; extravasation; intravasation; macrophage; metastasis; niche; premetastatic; seed; soil

Citation:

Akhtar, M., Haider, A., Rashid, S., Al-Nabet, A. Paget's "Seed and Soil" Theory of Cancer Metastasis: An Idea Whose Time has Come. *Advances in Anatomic Pathology*. 2019; Volume 26, Number 1, pp. 69-74

Impact Factor: 3.530

Classification of Endometrial Carcinoma: New Perspectives Beyond Morphology

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Abstract

Endometrial carcinoma has been traditionally divided into type 1 or endometrioid type that is usually moderate to well differentiated and type 2 that is usually poorly differentiated with high histologic grade and aggressive clinical behavior. However, interobserver diagnostic agreement is suboptimal, particularly among the high-grade histotypes. Furthermore, recent data indicate that this histotype assignment does not independently correlate with survival. In recent years, there has been remarkable progress in our understanding of the molecular basis of endometrial carcinoma and extensive molecular studies have been performed under The Cancer Genome Atlas Program (TCGA) leading to molecular classification of endometrial carcinoma that has been shown to be significantly prognostic. This classification system divides the tumors into 4 subgroups namely, polymerase **ε** exonuclease (POLE) ultramutated, hypermutated microsatellite instability, copy number low, and copy number high (serous-like). Carcinomas with POLE domain hotspot mutations are highly prognostically favorable; those with copy number alterations and TP53 mutations are highly aggressive; and microsatellite unstable and "copy number low" endometrioid are associated with intermediate prognoses. The TCGA applied methods that are too costly and cumbersome for widespread implementation into routine clinical practice. Several other groups have attempted to identify these categories by using immunohistochemical biomarkers rather than molecular studies. Immunohistochemical biomarkers have been used successfully to identify all the subgroups except for POLE ultramutated, which requires sequencing for proper categorization. It is hoped that future studies will identify a suitable biomarker for POLE mutation so that this classification can be routinely used in all medical centers.

Citation:

Akhtar M, Hyassat S, Elaiwy O, Rashid S. Classification of Endometrial Carcinoma: New Perspectives Beyond Morphology. *Advances in Anatomic Pathology* 2019; 26:421–427

Impact factor: 3.530

Intrinsic Molecular Subclassification of Urothelial Carcinoma of the Bladder: Are We Finally there?

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Abstract

Bladder cancer is a highly prevalent disease throughout the world usually encountered in older patients, and associated with substantial morbidity, mortality, and cost. The treatment of bladder cancer has remained unchanged for the last several decades. However, in recent years the availability of comprehensive genomic data from The Cancer Genome Atlas and other large projects have considerably improved our understanding of the pathogenesis of these tumors. These studies demonstrated that bladder cancers can be grouped into 2 broad categories namely basal and luminal molecular subtypes with recognizable subgroups in each of these categories. Clinical data suggest that invasive basal cancers are more sensitive to neoadjuvant chemotherapy (NAC), such that most patients with basal cancers who are aggressively managed with NAC have excellent outcomes. Patients with luminal cancers do not appear to derive much clinical benefit from NAC, but some may appear to be sensitive to anti-programmed death-ligand 1 (PDL1) antibodies and possibly other immune checkpoint inhibitors. It is hoped that future studies will also identify biomarkers such as immunohistochemical markers which may be used to predict therapeutic response of these tumors. This will contribute substantially toward efficient and cost-effective diagnosis and management of these neoplasms.

Citation:

Akhtar M, Al-Bozom IA, Ben Gashir M, Taha NM. Intrinsic Molecular Subclassification of Urothelial Carcinoma of the Bladder: Are We Finally there? *Advances in Anatomic Pathology*. 2019 ;26(4):251-256.

Impact Factor: 3.53

Tight Junction Proteins and Signaling Pathways in Cancer and Inflammation: A Functional Crosstalk

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Abstract:

The ability of epithelial cells to organize through cell-cell adhesion into a functioning epithelium serves the purpose of a tight epithelial protective barrier. Contacts between adjacent cells are made up of tight junctions (TJ), adherens junctions (AJ), and desmosomes with unique cellular functions and a complex molecular composition. These proteins mediate firm mechanical stability, serves as a gatekeeper for the paracellular pathway, and helps in preserving tissue homeostasis. TJ proteins are involved in maintaining cell polarity, in establishing organ-specific apical domains and also in recruiting signaling proteins involved in the regulation of various important cellular functions including proliferation, differentiation, and migration. As a vital component of the epithelial barrier, TJs are under a constant threat from proinflammatory mediators, pathogenic viruses and bacteria, aiding inflammation and the development of disease. Inflammatory bowel disease (IBD) patients reveal loss of TJ barrier function, increased levels of proinflammatory cytokines, and immune dysregulation; yet, the relationship between these events is partly understood. Although TJ barrier defects are inadequate to cause experimental IBD, mucosal immune activation is changed in response to augmented epithelial permeability. Thus, the current studies suggest that altered barrier function may predispose or increase disease progression and therapies targeted to specifically restore the barrier function may provide a substitute or supplement to immunologic-based therapies. This review provides a brief introduction about the TJs, AJs, structure and function of TJ proteins. The link between TJ proteins and key signaling pathways in cell proliferation, transformation, and metastasis is discussed thoroughly. We also discuss the compromised intestinal TJ integrity under inflammatory conditions, and the signaling mechanisms involved that bridge inflammation and cancer.

Keywords:

claudin; metastasis; signaling molecules; tight junction; tumor

Citation:

Bhat, A. A., Uppada, S., Achkar, I. W., Hashem, S., Yadav, S. K., Shanmugakonar, M., Al-Naemi, H. A., Haris, M., & Uddin, S.Tight Junction Proteins and Signaling Pathways in Cancer and Inflammation: A Functional Crosstalk. *Frontiers in physiology*, 2019, 9, 1942.

Impact Factor: 3.201

Testosterone, testosterone therapy and prostate cancer

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Abstract

With prostate cancer not observed in eunuchs and total androgen suppression by castration an effective first-line treatment for advanced prostate cancer, the dramatic regression seen in tumor symptoms after castration, lead to the theory that high levels of circulating androgens were a risk factor for prostate cancer. This theory however, ignored the effects testosterone variations within a physiologic range could have on early tumor events and since the early 2000s, clinical evidence discounting testosterone as a linear mechanistic cause of prostate cancer growth mounted, with alternative mechanistic hypotheses such as the saturation model being proposed. Together with a growing understanding of the negative health effects and decreased quality of life in men with testosterone deficiency or hypogonadism, a paradigm shift away from testosterone as a prostate cancer inducer occurred allowing clinicians to use testosterone therapy as potential treatment for men with difficult and symptomatic hypogonadism that had been previously treated for prostate cancer. In this review we contextualise the idea of testosterone as a risk factor for prostate cancer inducement and compile the most current literature with regards to the influence of testosterone and testosterone therapy in prostate cancer.

Keywords:

Hypogonadism; prostate cancer; quality of life; testosterone

Citation:

A. Yassin, K. AlRumaihi, R. Alzubaidi, S. Alkadhi & A. Al Ansari, Testosterone, testosterone therapy and prostate cancer, *The Aging Male*, 2019, 22:4, 219-227

Impact factor: 2.5

Functional magnetic resonance imaging of head and neck cancer: Performance and potential

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Abstract

Functional magnetic resonance imaging (MRI) of tumors of the head and neck usually encompasses diffusion-weighted imaging (DWI) and intravenous (IV) contrast T1 dynamic perfusion imaging (DCE-MRI or PWI). Both techniques can characterize different tissues by probing into their microstructure, providing a novel approach in oncological imaging. In this pictorial review, we will cover the important technical aspects of DWI and PWI, the pathophysiological background and the current applications and potential of these functional MRI techniques in the imaging of head and neck cancer.

Keywords:

Diffusion-weighted MRI, functional MRI, head and neck cancer, post-contrast dynamic MRI

Citation:

El Beltagi AH, Elsotouhy AH, Own AM, Abdelfattah W, Nair K, Vattoth S. Functional magnetic resonance imaging of head and neck cancer: Performance and potential. *The Neuroradiology Journal*. 2019;32(1):36 52.

Impact Factor: 2.370

What Are the Challenges and Facilitators for Implementing a 24-Hour Telephone Cancer Service in Qatar? A Literature Review

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Abstract

Objective: To identify the challenges and facilitators for implementing a 24-h telephone cancer service. **Data sources:** English language articles were retrieved from Medline, Cumulative Index of Nursing and Allied Health Literature, and Ovid Nursing electronic databases published from 2000 to 2015. **Study Design:** The authors performed an integrative literature review. The qualitative and quantitative articles were evaluated using the Critical Appraisal Skills Program. All mixed-methods articles were evaluated using the Mixed Methods Appraisal Tool. Thematic analyses were used to synthesize the findings from the included articles. **Findings:** The literature of this review highlights the complexity of the decisions that accompany the consideration of implementing a teleoncology in Qatar. The literature review detailed challenges and facilitators for implementing 24-h call service for cancer patients. These were grouped as human, technology, documentary tools, and organizational domains. The core concept that integrates each of these domains is communication. **Conclusions:** If the telephone triage is to be implemented in National Center for Cancer Care and Research (NCCCR), more research is needed about the characteristics of cancer patients in Qatar. A more robust understanding of this population will inform decisions about the utility of developing a teleoncology service at NCCCR.

Citation:

Zawahreh A., Rankin J., Abu Jaber A., and Nashwan A. What Are the Challenges and Facilitators for Implementing a 24-Hour Telephone Cancer Service in Qatar? A Literature Review. *Telemedicine and e-Health*. 2019. 25(8):678-685.

Impact Factor: 1.996

Cohort Study of Immunotherapy in Patients with Colorectal Cancer and DNA Mismatch Repair Defects

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Abstract

Colorectal cancer (CRC) is the second leading cause of cancer related deaths after lung cancer and it is the third most commonly diagnosed malignancy worldwide after the lung and the breast. Immunotherapeutic agents such as checkpoint inhibitors had a FDA approval, this therapeutic approach for patients with CRC is still under development and there are more studies ongoing using checkpoint inhibitors in phase II and phase III evaluating the efficacy of these agents in patients with deficient mismatch repair (d MMR). In 15% of the CRCs there are defective DNA mismatch repair systems (MMR) caused by inactivation of mutL homologue 1 (MLH1), MLH3, mutS homologue 2 (MSH2), MSH3, MSH6, or PMS1 homologue 2 (PMS2). This may occur through inherited or sporadic mutations, or through epigenetic silencing. These dominant genomic features give rise to hyper mutations and microsatellite instability (MSI) In this study we used checkpoint inhibitors in 3 patients, (2 colon and 1 rectal cancer), one of them with metastatic stage as palliative treatment, 1 as neo adjuvant before liver metastasis resection then as adjuvant and the 3rd one as neo adjuvant after chemo radiotherapy for rectal cancer, all of the 3patients showed dramatic response. 2.

Keywords:

Colorectal cancer (CRC); Immunotherapy; Microsatellite instability (MSI); Mismatch repair deficient (dMMR)

Citation:

Rasul KI, Cohort Study of Immunotherapy in Patients with Colorectal Cancer And dna Mismatch 2 Repair Defects. *Japanese Journal of Gastroenterology and Hepatology*. 2019; V2(5):1-5.

Impact Factor: 1.69

Diabetes-induced Proteome Changes Throughout Development

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Abstract

Background: Diabetes Mellitus (DM) is a multisystemic disease involving the homeostasis of insulin secretion by the pancreatic islet beta cells (β-cells). It is associated with hypertension, renal disease, and arterial and arteriolar vascular diseases.

Discussion:

The classification of diabetes is identified as type 1 (gene linked -cell destruction in childhood) and type 2 (late onset associated with -cell overload and insulin resistance in peripheral tissues. Type 1 diabetes is characterized by insulin deficiency, type 2 diabetes by both insulin deficiency and insulin resistance. The former is a genetically programmed loss of insulin secretion whereas the latter constitutes a disruption of the homeostatic relationship between the opposing activity of β- cell insulin and alpha cell (α-cell) glucagon of the Islets of Langerhans. The condition could also occur in pregnancy, as a prenatal occurring event, possibly triggered by the hormonal changes of pregnancy combined with β-cell overload. This review discusses the molecular basis of the biomolecular changes that occur with respect to glucose homeostasis and related diseases in DM. The underlying link between pancreatic, renal, and microvascular diseases in DM is based on oxidative stress and the Unfolded Protein Response (UPR).

Conclusion: Studying proteome changes in diabetes can deepen our understanding of the biomolecular basis of disease and help us acquire more efficient therapies.

Keywords:

Diabetes mellitus; endoplasmic reticulum stress; organogenesis; proteome; stress signaling; unfolded protein response.

Citation:

Dina J., Ahmed S. M., Al-Dewik N., Bahbah E. I., Omar N. H., Mustafa M., Salman D.O. et al. "Diabetes-Induced Proteome Changes Throughout Development." *Endocrine, Metabolic & Immune Disorders-Drug Targets* (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders, 2019, 19, 6: 732-743.

Impact Factor: 1.160

Giant Parathyroid Adenoma: A Case Report and Review of the Literature

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Abstract

Background: Giant parathyroid adenoma is a rare type of parathyroid adenoma defined as weighing > 3.5 g. They present as primary hyperparathyroidism but with more elevated laboratory findings and more severe clinical presentations due to the larger tissue mass. This is the first reported case of giant parathyroid adenoma from the Middle East.

Case presentation: A 52-year-old Indian woman presented with a palpable right-sided neck mass and generalized fatigue. Investigations revealed hypercalcemia with elevated parathyroid hormone and an asymptomatic kidney stone. Ultrasound showed a complex nodule with solid and cystic components, and Sestamibi nuclear scan confirmed a giant parathyroid adenoma. Focused surgical neck exploration was done and a giant parathyroid adenoma weighing 7.7 gm was excised.

Conclusions: Giant parathyroid adenoma is a rare cause of primary hyperparathyroidism and usually presents symptomatically with high calcium and parathyroid hormone levels. Giant parathyroid adenoma is diagnosed by imaging and laboratory studies. Management is typically surgical, aiming at complete resection. Patients usually recover with no long-term complications or recurrence.

Keywords:

Atypical parathyroid adenoma; Giant parathyroid adenoma; Minimal invasive parathyroidectomy; Parathyroidectomy; Primary hyperparathyroidism.

Citation:

Al-Hassan MS, Mekhaimar M, El Ansari W, Darweesh A, Abdelaal A. Giant parathyroid adenoma: a case report and review of the literature. *Journal of Medical Case Reports*. 2019;13(1):332.

Impact Factor: 0.58

Abstracts

Dasatinib and Nilotinib As Upfront Therapy for Chronic-Phase Chronic Myeloid Leukemia (CML-CP) in Qatar: A Cost Effectiveness Analysis (CEA)

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Abstract

Objectives: Many tyrosine kinase inhibitors (TKIs) are approved for treating the chronic phase of chronic myeloid leukemia (CML-CP). This study aims at identifying the optimal upfront TKI treatment strategy; considering cost-effectiveness for CML patients from Qatar healthcare system perspective. Evaluated strategies included the newer generation TKIs; dasatinib 100 mg once daily and nilotinib 300mg twice daily. We evaluated both treatments considering their molecular and cytogenetic response outcomes at 12 months follow up as well their respective acquisition costs. **Methods:** A decision tree model was developed linking clinical effectiveness (defined as major molecular response MMR and/or complete cytogenetic response CCyR), utility, and cost data over a 12-months period. The choice of 12 months period is due to the evidence that the degree of short-term molecular and cytogenetic responses at certain follow- up times is correlated with CML prognosis. Patients who achieve a CCyR are shown to have high remission rates as well overall survival (OS) rates. Patients with newly diagnosed CML are adopted from Qatar Cancer Registry.The probability of primary clinical outcome is calculated from DASISON (dasatinib) and ENESTnd (nilotinib) trials. Direct healthcare costs were derived from the national healthcare payer system, whereas ADR data were derived from local incident reporting system. **Results:** In the first-line treatments of CML patients, with greater MMR (39% nilotinib vs 12% dasatinib) and CCyR (24% nilotinib vs 16% dastinib) response outcomes, and more adverse drug reactions (ADR) than dasatinib (13.3% vs 4%), nilotinib use is more cost effective with annual costs (QAR 232,102) and after 12 months follow up. Despite the lower acquisition annual cost of dasatinib (QAR 217,125), the incremental cost effectiveness ratio (ICER) of nilotinib versus dasatinib per MMR/CCyR achieved was 56,506 QAR per year. There were no cases in both arms that progressed to accelerated or blast phase. At a threshold of 3 times GDP per capita of Qatar and according to WHO recommendation, the nilotinib use is still cost-effective.

Limitations: For the surrogate outcome, we only consider the percentage of patients with or without MMR / CCyR response at 12 months. Nevertheless, we do not consider the depth and the duration of the MMR or CCyR. **Conclusions:** Upfront therapy of CML-CP patients by nilotinib plan appears to be more cost-effective than dasatinib. Although local real-life data for the effectiveness of these drugs are still warranted. The results of this study implying that nilotinib would be advantageous as first-line treatment for CML-CP patients from Qatar healthcare system perspective. Disclosures No relevant conflicts of interest to declare.

Citation:

Adel, Ahmad M, Dina Hamdi Abushanab, Anas Hamad, Mohammad Abdul-Jaber Abdulla and Mohamed A. Yassin. "Dasatinib and Nilotinib As Upfront Therapy for Chronic-Phase Chronic Myeloid Leukemia (CML-CP) in Qatar: A Cost Effectiveness Analysis (CEA)." (2019). *Blood*, 2019; 134 (Supplement_1): 5850.

Impact Factor: 16.562

Identification of a novel promiscuous anti-NY-ESO-1 immunogenic CD4+ peptide containing a CD8+ T-cell epitope highly present in metastatic gastric cancer responding to combined radiotherapy/ anti-PD-1 immunotherapy

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Abstract

Background: Immune checkpoint inhibitors offer the prospect of long-term disease control in solid tumor types. NY-ESO-1 is a cancer-testis antigen expressed by 20% of advanced gastric cancers, known to induce humoral and cellular immune responses. Combination of anti-PD-1 with radiotherapy is currently investigated. Radiotherapy has the ability to promote immunogenic cell death leading to the release of tumor antigens, increasing infiltration and activation of T cells. In this study, we investigated the immune response to the NY-ESO-1 antigen in metastatic gastric cancer treated with anti-PD-1 (pembrolizumab). **Methods:** T cells response to the NY-ESO-1 antigen was investigated by ELISPOT against NY-ESO-1 PepMix, against the 43 single peptides overlapping the NY-ESO-1 whole protein and the NY-ESO-1 HLA-A2 restricted peptide. The IEDB1 prediction database was used to predict the patient's HLA DR, DQ and DP binding to NY-ESO-1. We subsequently characterized the phenotypic and functional activity of the patient T cells using flow cytometry analysis. **Results:** We have identified a novel promiscuous immunogenic NY-ESO-1 peptide restricted to the 4 HLA-DQ and HLA-DP alleles and containing the known NY-ESO-1 HLA-A2-02:01 (P157-165) immunogenic epitope. CD8þ T cells were increased during combined therapy and at disease resolution in which its PD-1þCD8þ subset was increased during combined therapy and resolution then decreased at disease progression. The CD107þ cytotoxic subset of the CD8þ/HLA-A2-NY-ESO-1-dextramerþ T cells were markedly increased during combined therapy and at resolution then dramatically decreased at re-progression. **Conclusion:** We have identified a novel promiscuous anti-NY-ESO-1 immunogenic CD4þ peptide containing the P157-165 HLA-A*02:01/CD8þ epitope that was highly presented at disease resolution and decreased at progression after combined radiotherapy/anti-PD-1 immunotherapy. Our study

showed that radiation therapy combined with immune checkpoint blockade would enhance the immune response that correlates with the patient clinical outcome.

Citation:

M Merhi, A Raza, V Inchakalody, S Sivaraman, F Panayampilly, S Mestiri, S Hydrose, N Allahverdi, M Jalis, A Relecom, L Al Zaidan, J Feilchenfeldt, M S Elkhatim Hamid, M Mostafa, A R Zar Gul, S U Khan, S Dermime, 112P Identification of a novel promiscuous anti-NY-ESO-1 immunogenic CD4+ peptide containing a CD8+ T-cell epitope highly present in metastatic gastric cancer responding to combined radiotherapy/anti-PD-1 immunotherapy, *Annals of Oncology*, 2019, Volume 30, Issue Supplement_11,

Impact Factor: 14.196

A phase I clinical trial of malignant pleural mesothelioma treated with locally delivered autologous anti-FAP-targeted CAR T-cells

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Abstract

Background: Malignant pleural mesothelioma (MPM) is a cancer with a worldwide increasing incidence due to the use of asbestos. MPM is incurable despite the use of multimodality treatment. Tumor spread confined to the thoracic cavity is a hallmark of MPM, providing a rational for local treatment. We developed a chimeric antigen receptor (CAR) targeting FAP (fibroblast activating protein), a cell-surface antigen that we have shown to be highly expressed in epithelial cancers. Method: Using a Δ-CD28-costimulated CAR, we initiated a phase I clinical trial (NCT01722149) to determine the safety and persistence of intra-pleural administered anti-FAP-CAR T cells in the periphery. A single dose of 1x 10^6 re-directed T cells was administered through a pleural catheter. Patients were monitored on an intensive care unit for 48h. Clinical evaluations of on-target and off-tumor toxicity were assessed for 3 months. Laboratory analyses included cytokines, CRP and the detection of CAR-T cells in the pleural effusion and blood over time. Radiological evaluation with PET-CT scans was performed as standard of care. Results: Three patients with metastatic MPM were treated (all patients received at least two cycles of chemotherapy previous to CAR T-cell administration). No CAR T-cell-related toxicities were observed. Intense monitoring for cytokine release syndrome showed significant changes on a subset of cytokines. CAR T-cells were detected in the peripheral blood after treatment. Activity of the patient's redirected T cells was confirmed in vitro. Furthermore, one patient received an anti-PD1 checkpoint blockade antibody 8 months after CAR T-cell instillation with no toxicity. With a median follow-up of 18 months, 2 out of 3 patients are alive. Conclusions: In this phase I clinical trial, intra-pleural administration of anti-FAP CAR T-cells was well tolerated without any evidence of treatment related toxicity. Persistence

of CAR T-cells was documented in the periphery.

Citation:

A. Curioni, C. Britschgi, S. Hiltbrunner, L. Bankel, P. Gulati, W. Weder, I. Opit, O. Lauk, C. Caviezel, A. Knuth, C. Münz, C. Renner, R.A. Stahel, U. Petrausch, A phase I clinical trial of malignant pleural mesothelioma treated with locally delivered autologous anti-FAP-targeted CAR T-cells, *Annals of Oncology*, 2019, 30 (suppl_5): v475-v532.

Impact factor: 14.196

Uterine sarcomas in Qatar: Clinico-pathological characteristics and treatment outcome

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Abstract

Background: Uterine sarcomas (US) are a rare, heterogeneous group of malignancies that have rapid progressive clinical course and poor prognosis. We are reporting a retrospective review of clinico-pathological characteristics and outcome of therapy of these tumors in Qatar.

Methods: Retrospective records of 37 patients with US treated in Qatar between January 2010 and December 2016 were reviewed. They were stratified according to the age at diagnosis, menopausal status, ethnic group, pathological subtype of the tumor, grade, stage and treatment modalities (single vs combined modalities; surgical procedure, radiotherapy treatment, adjuvant and palliative chemotherapy. Diagnostic and pathology work was done in one facility. Treatment plan was discussed in MDT. The surgical treatment options were TAH with our without BSO. The chemotherapy we used is Docetaxel Gemcitabine in adjuvant setting as well as palliative treatment for metastatic cases. Radiotherapy was conducted via external beam irradiation followed by brachytherapy. Overall survival (OS) was obtained from the date of diagnosis to the date of death. For the patients who were alive, data was censored on the date of last follow up visit.

Results: For the reviewed 37 patients, the range of age was 23-64 years old with median age 47 years. LMS are representing the most frequent subtype seen in 15 patients (40%), ESS- 10 (28%), RMS 6 (16%), MMMT 2 (4 %) and non-specified 4 (12%). The stage of the disease at time of diagnosis was 1 in 26%, stage II in 48%, stage III in 11% and stage IV 15%. Total 23 patients underwent surgical resection, 12 patients (53%) simple hysterectomy and 11 (47%) TAH+BSO with LN dissection. 13 patients received chemotherapy, in 7 cases as adjuvant, in 4 combined with radiotherapy and in 2 cases as palliative. 13 patient received radiotherapy and brachytherapy. Median follow up time was 42 months. Thorough the time 10 patients died, 18 are still alive and 9 have lost follow up. The Kaplan Maier Curve showed median OS 40 months. Survival rate after one year was 79% and after 3 years 58%.

Conclusions:

In this pattern of population where the majority of US presented in early stages (74%), 42% will die within the first 3 years which reflect the need for running big phase 3 trials for optimization of the treatment approaches.

Citation:

Fadlelseid A.A., Ghazouani H.M.R., Saadi W.A.L.,Omar N., Al Malik H., Uterine sarcomas in Qatar: Clinico-pathological characteristics and treatment outcome. *Annals of Oncology*. 2019, Volume 30, Supplement 9, Page ix85

Impact factor: 14.196

5- AZA treatment induces cytotoxicity and in vitro expression of immunogenic NY-ESO-1 antigen in non-small lung cancer cell NCI-H1975

Varghese Inchakalody[1], Sara Taleb[1], Shereene Sherif[1], Queenie Fernandes[1], Mohammed Sahir Fairooz Panayampilly[2], Siveen Kodappully Sivaraman[2], Abdul Quaiyoom Khan[2], Vidhya Sadhasivan Nair[3], Asma A. El-Ashi[3], Lobna Al-Zaidan[1], Ahmed Iskandarani[2], Roopesh Krishnankutty[2], Lubna Therachiyil[2], Afsheen Raza[1], Maysaloun Merhi[1], Shehab Uddin[2,] Eyad Elkord[3], Said Dermime[1]

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Abstract

Background: Lung cancer is a major threat to the world and 80% of the reported cases belong to non-small cell lung cancers. Epigenetic modifications are common in lung cancers but can be reversible by using demethylating agents such as 5-AZA. Through our present study, we hypothesized that treatment with 5-AZA may induce the apoptosis and expression of immunogenic NY-ESO-1 antigen in NCI-H1975 cells. Apoptotic cell death would help to release the induced NY-ESO-1 protein which in turn could trigger T cells mediated immune responses. Methods: NCI-H1975 cells were treated with incrementing concentrations (1 to 10mM) of 5-AZA. Cytotoxicity was measured using real-time cell analyzer assay (RTCA). Apoptosis and cell cycle analysis were measured by flow cytometry and western blot. A proteomic profiling was carried out using label-free mass spectrometry. Bisulfite sequencing was performed for NY-ESO-1 gene and expression at mRNA and protein level was analyzed using qRT-PCR, cellular ELISA. Results: RTCA data revealed that 5-AZA treatment reduced cell proliferation at 120 h which was opted for comparative study. Flow cytometry showed an induction of apoptosis and a cell-cycle arrest at Sub-G0 phase. Western blot analysis confirmed the abstracts Annals of Oncology xi14 | Cell Therapy Volume 30 | Supplement 11 | December 2019 induction of apoptotic marker proteins such as cleaved Caspase3, Caspase8, PARP and BAX. We also observed that 31 proteins responsible for the induction of apoptosis were upregulated and 18 proteins linked to cell proliferation and metastasis were downregulated. Bisulfite sequencing revealed demethylation of the promoter of NY-ESO-1 gene and showed an induced expression of NY-ESO-1 protein and mRNA levels. Conclusion: Our study shows that 5-AZA cytotoxic effect would induce the expression of the immunogenic NY-ESO-1 antigen leading to activation of T cells mediated immune response. Our data infers the potential use of 5-AZA for lung cancer treatment.

Citation:

V P Inchakalody, S Taleb, S Sherif, Q Fernandes, F Sahir, S K Sivaraman, A Q Khan, V Sasidharan Nair, E A A Ashi, L S Al-Zaidan, A Iskandarani, R Krishnankutty, L Therachiyil, A Raza, M Merhi, S Uddin, E Elkord, S Dermime, 45P 5-AZA treatment induces cytotoxicity and in vitro expression of immunogenic NY-ESO-1 antigen in non-small lung cancer cell NCI-H1975, *Annals of Oncology*, 2019, Volume 30, Issue Supplement_11

Impact Factor: 14.196

Evaluation of Pulmonary Function in Patient with Transfusion Dependent Beta Thalassemia with Severe Iron Overload

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Abstract

Background; Transfusion-dependent β-thalassemia (TDT) is a severe form of congenital anemia. Regular blood transfusion and continual administration of iron-chelators are conventional therapeutic strategies in TDT. Despite progressive advancements in developing various iron scavenging drugs, iron overload is still considered a challenging conundrum in these patients. Multiple organ dysfunctions result from the toxic effect of excess iron deposition in parenchymal tissues that cause high morbidity and mortality among TDT patients. The greatest affected tissues include endocrine glands, liver, heart, and kidneys. Aim of the study: To investigate pulmonary function of patients with TDT in relation to their iron overload. Patients and Methods: Pulmonary function tests were done for 10 Patient with TDT (table 1) in a well-equipped lung function unit in a tertiary care hospital by experienced respiratory technicians. An ideal test session was taken up following ATS/ERS recommendations. A proper grading system including acceptability and repeatability criteria was applied. Measurement of DLCO is done with a technique of single breath carbon monoxide (CO) uptake in the lung and lung volume is measured with gas dilution and body plethysmography. Chest x ray (CXR) was obtained in all patients. Pulmonary function test was classified according to the following categories based on ATS/ERS criteria and American medical association criteria (AMA); Normal: FEV1/FVC more than 70% FEV1, FVC, TLC, RV and DLCO normal (at least 80% predicted)Obstructive: FEV1/FVC less than 70% FEV1 and FVC (less than 80% predicted). TLC and RV either normal or elevated (at least 120% predicted). DLCO normal (at least 80% predicted)Restrictive: FEV1/FVC ratio (more than 70%) (1) FEV1, FVC, and TLC decreased (no more than 80% predicted) and a decrease in DLCO (no more than 80% predicted) or (2) TLC and RV decreased (no more than 80% predicted) with normal DLCO, FEV1, FVC, and FEV1/FVC, suggestive of low lung volumes, or (3) reduced TLC and DLCO.Mixed obstructive and restrictive: FEV1/FVC ratio reduced, suggestive of obstructive disease. TLC and RV reduced, suggestive of restrictive disease. DLCO normalIsolated low DLCO: DLCO decreased with normal FEV1, FVC, FEV1/FVC, TLC, and RV (As per AMA DLCO less than 75% were considered abnormal) Results: In our 10 TDT patients 9 had normal CXR. One patient had minimal patchy ground glass opacity. Six patients (60%) had abnormally low DLCO indicating some impairment at the level of alveolar capillary membrane. None of them had obstructive pattern. However, 2 patients had

some air trapping. DLCO, DLCO/Hb, DLCO/VA and RV were correlated negatively with LIC (fig 1). PFTs (DLCO, RV, and TLC) were correlated negatively with the LIC. In addition, FEV1 and FVC were correlated negatively with ferritin level ($r = -0.7$ and -0.77 respectively, $p < 0.01$) (fig2). Discussion: we documented a significant alveolar capillary membrane dysfunction in a good number of asymptomatic patients with TDT. This dysfunction appears to increase with advance of age. Iron deposition in the lung parenchyma appears to be the etiology of this abnormality as supported by the significant negative correlations between PFT parameters on the one hand and LIC and ferritin level on the other hand. Conclusions: Substantial alveolar capillary membrane dysfunction occurs in a good number of asymptomatic patients with TDT which is correlated with the degree of iron overload. Further studies are required to confirm these abnormalities on a large scale. Disclosures No relevant conflicts of interest to declare.

Citation:

Yassin M. A, Ahmad M., Mohamed S., Yassin K.S, Nashwan A. J., Desanctis V., Soliman A.T.; Evaluation of Pulmonary Function in Patient with Transfusion Dependent Beta Thalassemia with Severe Iron Overload. Blood 2019; 134 (Supplement_1): 4818. *Blood* 2019, 134(Supplement_1):4818-4818

Impact Factor: 10.660

Evaluation of the Use of a Single Dose Rasburicase in Prophylaxis and Management of Tumor Lysis Syndrome (TLS) Among Cancer Patients in Qatar

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Abstract

Introduction: Rasburicase is a urate oxidase enzyme used for prophylaxis and treatment of hyperuricemia associated with TLS. The recommended dose of rasburicase is 0.2 mg/kg/day for 5 days; however, recent studies have demonstrated the effectiveness of a single rasburicase dose in prophylaxis and management of hyperuricemia associated with TLS. Our institution's TLS guideline was updated to recommend the use of a single rasburicase dose (0.2 mg/kg). The primary objective of this study was to assess the efficacy of a single rasburicase dose in controlling uric acid (UA); the secondary objective was to evaluate the impact of the institutional TLS guidelines update on consumption and cost of rasburicase. **Methods:** This is a single center retrospective cohort study including all patients who received rasburicase from August 2012 to March 2016 at the National Center for Cancer Care and Research (NCCCR) in Qatar. Patients were divided into 2 groups based on the prescribed number of rasburicase doses (single dose vs multiple doses). Collected data included patients' diagnosis, laboratory parameters rasburicase dose, duration, and number of dispensed vials. UA levels within 24 hours and on day 5 of initial rasburicase dose were evaluated. Risk stratification was determined according to institutional guidelines based on disease, white blood cell count, lactate dehydrogenase level, renal function, and UA level. **Results:**A total of 103 patients who received rasburicase were evaluated retrospectively; rasburicase was prescribed as single dose for 65 patients (63%) and multiple doses for 38 patients (37%). The majority of patients who received rasburicase as single or multiple doses were at high risk of developing TLS, representing 68% and 84%, respectively. Baseline mean UA levels were similar in both groups: 5.4±2.9 mg/dL vs 4.7±3.2 mg/L respectively (P=.7). Normal or undetectable UA levels were observed within 24 hours in 98% of patients in the single dose group and 100% of patients in the multiple doses group. All patients in both groups had normal UA on day 5 of rasburicase with relatively similar UA levels: 1.5±1.2 mg/dL vs 0.8±1 mg/dL (P=.18). Rasburicase consumption and cost were reduced by 42.5% after the guidelines update. **Conclusion:** The single rasburicase dose demonstrated efficacy in controlling serum UA levels. Updating the institutional TLS guidelines had a significant impact on rasburicase consumption and led to significant cost reduction.

Citation:

Kassem, N., El Omri, H., Yassin, M., & Elazzazy, S. Evaluation of the Use of a Single Dose Rasburicase in Prophylaxis and Management of Tumor Lysis Syndrome (TLS) Among Cancer Patients in Qatar, *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*, 2019, *17*(3.5)

Impact Factor: 7.140

Barriers and Trends in Cancer Patients' referrals to Pain Management in Qatar: A Randomized Cohort Prospective Study

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Abstract

Background: Studies showed that 40%–50% of patients with cancer pain receive insufficient analgesia due to different factors (Beyeler et al, Support Care Cancer 2008; Salminen et al, Support Cancer Care 2008), beside the challenges to accurately assess pain, which might affect drug selection and pain control (Stewart, Ulster Med J 2014). In NCCCR, the treating primary physicians (PP) may prescribe analgesics to their patients or refer them to the Pain Management Team (PMT), based on evaluation or as requested by patients. This study will address the clinical concerns of PP, which may lead to refer the patients to PMT, moreover the clinical judgement of PMT on the referred cases whether they need to be refereed or not. Objectives: To determine the efficiency of the referral pathway to the pain clinic by PMT. Methods: PMT is going to assess the referred patient to their clinics according to pain assessment methods. Patients will be evaluated whether they have been appropriately referred or not, any unnecessary referral will be documented based on the following;

- If the patient was referred by hematologist or oncologist
- If the patient required specialized treatment
- If the patient required urgent treatment/prescription or advanced pain management techniques
- If the patient required further consultation by pain management
- If the patient could be managed by PP

Results: 195 patients were newly referred to the pain clinic during the period from March 8, 2018 to August 31, 2018. 12% (23/195) were deemed as unnecessary referrals based on PMT assessment; 43% (10/23) of them were hematology patients, while 57% (13/23) were oncology. The majority was for breast cancer and sickle cell disease patients with 35% for each. According to the PMT assessment, 61% (14/23) patients (95% CI, 40.79%–77.84%) considered unnecessary referrals due to improper basic pain assessment and management by PP, while 30% (7/23) patients (95%CI, 15.60%–50.87%) asked for refill medications. Conclusion: There is 12% unnecessary referrals to PMT, which need further improvement in the referral pathway, via the development of a definite referral criteria to PMT. PP should be encouraged to provide basic pain treatment and to consider multidisciplinary management with appropriate coordination for better

improvements in patients' quality of life.

Citation:

bdelwahab, R., Hamad, A., Azzaz, S., Okka, R., Wahid, M. A., Shibli, K., Geziry, A., Saleh, F., Rasul, K., & Saleem, W. Barriers and Trends in Cancer Patients' referrals to Pain Management in Qatar: A Randomized Cohort Prospective Study, Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw, 2019, 17(3.5)

Impact Factor: 7.140

Barriers and Trends in Cancer Patients` Pain Management in Qatar: A Randomized Cohort Prospective Study

Rehab Abdelwahab [1], Anas Hamad [1], Randa Al Okka [1], Mohd A. Wahid [1], Khalil Ullah Shibli [1], Wael Saleem[1], Ahmed El Geziry [1], Fathi Saleh [1], Kakil Rasul [1] and Shereen Elazzazy[1]

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Abstract

Background: Up to 70% of cancer patients experience pain during the course of illness (Fallon, Support Care Cancer 2008). Studies showed that 40%–50% of patients with cancer pain receive insufficient analgesia due to different factors. Physicians are facing different challenges to accurately assess pain which might affect drug selection and pain control (Beyeler et al, Support Care Cancer 2008; Salminen et al, Support Cancer Care 2008; Stewart, Ulster Med J 2014). In NCCCR, treating physicians may prescribe analgesics to their patients or refer them to the Pain Management Service (PMS) based on their evaluation or as requested by patients. This study explored the factors which might lead to undertreatment of cancer pain in Qatar. In addition, focused on cancer patients' pain management satisfaction and PMS awareness. Objectives: To assess the existing PMS at NCCCR from patients' perspective. Methods: In this study, we evaluated patients' pain management perception via a validated written (Arabic and English) questionnaire (SF-MPQ-2; available at https://eprovide.mapi-trust.org/instruments/short-form-mcgill-pain-questionnaire#DESCRIPTIVE_INFORMATION; Gauthier et al, J Pain 2014) and a structured interview by outpatient pharmacists at a single point of time, to assess patients` awareness towards the PMS, if they are receiving pain medications or not, if they are experiencing any pain regardless on pain medications or not, pain severity, and patients' level of satisfaction towards their medications. A sample of 400 patients was randomly selected amongst the total cancer population visiting NCCCR Pharmacy over a specific period of time. Participants were consented and interviewed. Results: 400 patients agreed to participate; the median age was 50. Male to female ratio was 3 to 7. Data showed that 61% (245/400) of participants were not aware of the existence of the PMS. Only 20% (78/400) were aware and followed by PMS, with a satisfaction rate of 76% (59/78). Although 69% (276/400) of the patients were on pain medications, only 70% (191/276) were satisfied with their current medications. However, from the satisfied patients, 57% (109/191) rated their pain as 4–10 at the time of interview (ATI). In the 31% (124/400) that were not taking any pain medications; 77% (96/124) didn't know about the PMS, and 44% (55/124) had 4–10 pain severity (ATI). Conclusion: These findings provide clear evidence that factors leading to undertreating of cancer pain in Qatar might be unawareness of the PMS existence, pain treatment by unspecialized physicians, and patients' reluctance to express their pain. Thus, raising patients' awareness and standardizing the referral criteria can improve pain control and quality of life amongst cancer patients.

Citation:

Abdelwahab, R., Hamad, A., Al Okka, R., Wahid, M. A., Shibli, K., Saleem, W., El Geziry, A., Saleh, F., Rasul, K., & Elazzazy, S. (). Barriers and Trends in Cancer Patients` Pain Management in Qatar: A Randomized Cohort Prospective Study, *Journal of the National Comprehensive Cancer Network J* Natl Compr Canc Netw, 2019, 17(3.5)

Impact Factor: 7.140

Once in a lifetime: a tale of many tumors and one endocrine site; the fascinating story of pituitary metastases: a case series

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Abstract

Objective: Metastases to the pituitary gland are extremely rare. Common tumors that metastasize are breast and gastrointestinal tumors. We present a case series of 5 cases. Methods: n/a Results: Five cases presented with DI, a lady 45 years of age who was diagnosed with breast carcinoma and on MRI and PET scan was found to have multiple secondary deposits in bones, liver and pituitary. She later developed frank symptoms of DI and was confirmed to have panhypopituitarism. The second case was 77-year-old male who presented with DI and on MRI scan was found to have thickening of the pituitary stalk, and on testing no other pituitary hormones were deficient but he had confirmed posterior pituitary deficiency.

Citation:

Mohamed M., Dabbous Z., Benjamin S., Green, F., Hassoun, S., et al. *Endocrine Practice, suppl.* 2019, SUPPLEMENT 1; Jacksonville Vol. 25, 250-251.

Impact Factor: 4.149

Prophylaxis and Management of Tumor Lysis Syndrome (TLS) Amongst Cancer Patients in Qatar: A Retrospective Cohort Study

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Abstract

Introduction: TLS is an oncological emergency caused by the breakdown of malignant cells resulting in massive release of cellular components into the blood. Rasburicase is a urate oxidase enzyme used for prophylaxis and treatment of hyperuricemia associated with TLS. Our institutional TLS guidelines were updated to recommend the use of a single dose rasburicase. Theobjective of the study was to assess the compliance to TLS guidelines, evaluate the effect of guidelines update on consumption and cost of rasburicase and assess the efficacy of a single rasburicase dose in lowering uric acid levels. Methods: It is a retrospective cohort study, including oncology and hematology adult patients who developed or were at risk of TLS in Qatar. The study included 103 patients divided into 2 groups based on the date of the TLS guidelines update; 48 patients before and 55 patients after the guidelines update. Results: The rate of compliance to the institutional TLS guidelines after the update increased from 77% to 87% (P=0.17), from 46% to 78% (P=0.001), and from 56% to 95% (P < 0.001) in terms of proper indication, proper duration and G6PD screening, respectively. Rasburicase consumption and cost were significantly reduced by 43% after the guidelines update. Furthermore, the single dose rasburicase was efficacious in controlling uric acid within 24 hours in 98% of patients. Conclusions: Updating the institutional TLS guidelines had a significant impact on compliance to guidelines and optimization of rasburicase use. Moreover, the use of a single rasburicase dose demonstrated efficacy in lowering serum uric acid levels.

Citation:

Kassem N., El Omri H., Yassin M. A., Elazzazy S., Prophylaxis and Management Of Tumor Lysis Syndrome (TLS) Amongst Cancer Patients In Qatar: A Retrospective Cohort Study, *Supportive Care in Cancer* 2019, 27(Suppl 1):S1–S302

Impact Factor: 2.860

Circulating Tumor Cells (CTCs) for Comprehensive and Multiregional Non-Invasive Genetic Characterization of Multiple Myeloma (MM)

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Abstract

Background: Genetic characterization is becoming relevant to predict risk of progression in smoldering MM and is fundamental to estimate survival in active MM. Thus, patients undergo multiple bone marrow (BM) aspirates for genetic screening that beyond painful, may not be fully representative due to patchy BM involvement, spatial genomic heterogeneity, or extramedullary disease. Accordingly, cell-free DNA has been investigated and showed high concordance with BM aspirates, but information is typically restricted to a few recurrent mutations since comprehensive genetic characterization (eg. whole-exome sequencing, WES) is applicable to <25% of MM patients (those with ≥10% tumor DNA). By contrast, CTCs are detectable in virtually all smoldering and active MM patients and their numbers are prognostically relevant, but their applicability for non-invasive genetic characterization of MM has been poorly investigated. Aim: To compare the genetic landscape of CTCs vs matched BM clonal plasma cells (PCs) and extramedullary (EM) plasmacytomas, and validate standardized assays for CTCs' detection, isolation and genetic characterization. Methods: We used EuroFlow next-generation flow (NGF) cytometry to detect and isolate peripheral blood (PB) CTCs and matched BM clonal PCs from 38 MM patients (25 at diagnosis and 13 at relapse). In 8 cases, clonal PCs from EM plasmacytomas were also FACSorted. PB T cells were always used as matched

germline control. In the training set, we performed custom WES (preceded by triplicates of whole-genome amplification) in matched CTCs, BM and EM clonal PCs from the 8 patients with all three spatially distributed clones. Only those mutations present in 2/3 libraries analyzed per sample were considered positive. In the validation set, we compared mutations, copy number alterations (CNA) and translocations present in CTCs and BM clonal PCs using the Chromium Exome Solution for low DNA-input (n=8), and solely CNA using the Affymetrix CytoScan HD platform (n=22). Read mapping, variant and structural calling were performed with the Multisample Exome (Dreamgenics) and LongRanger (10XGenomics) pipelines. The Chromosome Analysis Suite software (Affymetrix) was used to analyze CNA. Only those mutations with ≥10% variant allele frequency (VAF) and CNA larger than 1Mb were considered. Results: In the training set, 193/226 (85%) and 231/269 (86%) of total mutations present in BM and EM clonal PCs, respectively, were detectable on CTCs. All MM recurrent mutations (eg. *BRAF*) found in BM or EM clonal PCs were present in CTCs. Of note, there were 39 mutations in EM plasmacytomas that were detectable in CTCs but absent in BM clonal PCs. Furthermore, up to 50 mutations were present in CTCs while undetectable in BM clonal PCs (n=44) or EM plasmacytomas (n=6).After showing that CTCs harbor most mutations present in both medullary and extramedullary disease and even unveil mutations undetectable in single BM aspirates or individual EM plasmacytomas, we sought to evaluate the performance of standardized assays suitable to screen mutations and/or CNA from low cell numbers (ie. CTCs). Using 10XGenomics, 250/266 (94%) of total mutations and 17/17 (100%) of MM recurrent mutations present in BM clonal PCs were detectable on CTCs (eg. *KRAS, BRAF, TP53* or *FAM46C*). The VAF of private mutations ranged between 0.1 and 0.3, suggesting these were subclonal in their respective spatial regions. Using 10XGenomics, 101/119 (85%) CNA and 2/2 (100%) IgH Tx present in BM clonal PCs were detectable in CTCs. Using the Cytoscan HD, there was 100% concordance between CNA in CTCs and BM clonal PCs, both at the chromosomal arm and interstitial levels.All mutations in *TP53* were detectable in CTCs. Furthermore, +1q, del(1p), del(17p) or t(4;14) were always detected in CTCs whenever present in BM clonal PCs, and confirmed by FISH. Conversely, such comprehensive genetic characterization unveiled innumerous CNA and translocations not tested by routine FISH panels [eg. *MYC* amplification or t(6;14)]. Conclusions: Using two different standardized methods, we showed in the largest series in which CTCs were genetically characterized, that these are a reliable surrogate of MM patients' genetic landscape inside and outside the BM. Because NGF is broadly used, quantification, isolation and genetic characterization of CTCs may emerge as an optimal and standardized approach for non-invasive risk-stratification of MM patients.

Keyword:

circulating tumor cells, genetics, multiple myeloma, photon correlation spectroscopy, portacaval shunt, surgical, precordial catch syndrome, plasmacytoma, protein p53, cell-free dna, chromium

Citation:

Garcés, J. J., Bretones G., Burgos L., Valdés-Mas R., Alignani D., D. A. Sampedro Puente, Goicoechea I., Alvarez M. G., Gárate S., Rodriguez I., Calasanz M. J., Rodríguez P., Ríos R., Martínez-López J., Millacoy P., Palomera L., Del Orbe R., Perez A., Agirre X., Flores-Montero J., Sanoja-Flores L., Orfao A., El Omri H., Prósper F., López-Otín C., San-Miguel J. F. and Alves Faustino Paiva B. "Circulating Tumor Cells (CTCs) for Comprehensive and Multiregional Non-Invasive Genetic Characterization of Multiple Myeloma (MM)." *Blood,* 2019;134 (Supplement_1): 3064.

Impact Factor: 2.274

Role of lncRNAs as prognostic factor and potential therapeutic target in Multiple Myeloma

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Abstract

Deregulation of long non-coding RNAs (lncRNAs) is emerging as a common feature of human tumors, suggesting that their investigation may uncover novel oncogenic mechanisms. Previous studies suggested that the alteration of some lncRNAs might play an important role in multiple myeloma (MM); however, the complete expression landscape of lncRNAs has not been elucidated. In the present work we characterized the lncRNAs transcriptome of MM determining their potential involvement in this disease. Firstly, we performed paired-end strand-specific RNA-seq (ssRNA-seq) in 38 purified plasma cell (PC) samples from MM patients, 3 bone marrow PCs (BMPCs) of healthy donors, and in distinct normal B-cell populations (Naïve, Centroblasts, Centrocytes, Memory and Tonsilar PCs). We identified 40,511 novel lncRNAs, representing more than half of MM transcriptome (56%) and which, together with the previously annotated lncRNAs, comprised most of the MM transcriptome (82%). We studied the transcriptional heterogeneity

in MM, observing that lncRNAs showed a more heterogeneous expression than coding genes, suggesting that these elements could contribute to the heterogeneity of MM. To determine differentially expressed genes, each MM patient was compared to normal BMPCs, detecting 10,351 lncRNAs overexpressed and 9,535 downregulated in more than 50% of patients, focusing on a group of 989 lncRNAs specifically upregulated in MM (MM-specific lncRNAs), considering the B-cell populations. Next, we aimed to determine whether upregulation of those lncRNAs was under epigenetic control, analyzing the distribution of six histone marks (H3K4me3, H3K4me1, H3K27ac, H3K36me3, H3K27me3, and H3K9me3) by ChIP-seq. We compared MM cases to normal B-cell subtypes and detected 89 lncRNAs with de novo epigenomic activation and expression in MM, suggesting an epigenetic rewiring in MM. We focused on LINC-SMILO, de novo epigenetically active and expressed lncRNA in MM. Knockdown of LINC-SMILO in 3 different MM cell lines (MM.1S, MM.1R and KMS-11) by 2 different shRNAs resulted in reduced proliferation and induction of apoptosis, associated with activation of ERVs (Endogenous retroviruses) and increase in interferon induced genes (measured by MARS-seq), which results in the activation of Interferon pathways, essential for MM cells survival. Finally, we aimed to determine whether lncRNAs could improve the current prognostic of MM patients. Using the IA11 release of CoMMpass data, we analyzed lncRNAs by COX regression and Backward elimination of Stepwise regression analysis, obtaining that the overexpression of the lncRNA PDLIM1P4 together with 1q amplification and 17p deletion stratified MM patients in three different risk groups. In summary, our study shows the complexity of lncRNA transcriptome in MM, and suggests that some of these lncRNAs have prognostic influence or can be used as potential therapeutic targets for MM.

Citation:

Carrasco-Leon A., Ezponda T., Meydan C., Valcárcel L., Ordóñez R., Kulis M., Garate L., Miranda E., Segura V., Guruceaga E., Vilas-Zornoza A., Alignani, D., Castro-Labrador L., Pascual M., Amundarain, A., Omri H., Taba, R., Calasanz M., Planes F., Prosper F., Role of lncRNAs as prognostic factor and potential therapeutic target in Multiple Myeloma. *Clinical Lymphoma Myeloma and Leukemia.* 2019. Volume 19, Issue 10, Supplement e354-e355.

Impact factor: 2.274

Conference Presentations

Title	Research team	Conference
Sarcoma Awareness Day 16 January 2019		
Subcutaneous Nematode Mimicking Soft Tissue Neoplasm	Khaled Murshed, Rayan Sibira, Adham Ammar	Sarcoma Awareness Day., Medical Education, Doha, Qatar16 January 2019
Malignancy in giant cell tumor of bone: A case of rapid transformation in an unprecedented site	Orwa Elaiwy, Adham Ammar	Sarcoma Awareness Day January 16th, 2019
4th Inter-Professional Education Day, QU, Qatar Jan. 26th, 2019,		
A decade of Inter-professional Collaboration VTE Prophylaxis; Challenges and Success in NCCCR	Shereen Elazzazy, Rehab Abd El Wahab, Lamiaa Saleh, Anad Hamad	4th Inter-Professional Education Day, Jan. 26th, 2019, QU, Qatar
The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar 6-8 Feb. 2019		
Evaluation of Cisplatin Induced Ototoxicity and Cardiotoxicity amongst Adult Cancer Patients in Qatar. A Retrospective Cohort Study	Rawan A. Dawoud, Farah Jibril, Shereen Elazzazy	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019.
"Regorafenib safety profile among Adult Cancer Patients in Qatar. A Retrospective Cohort Study	Sahar Nasser, Anas Hamad, Shereen Elazzazy	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019.
Evaluation of Palbociclib Use in Qatar: A Retrospective Analysis	Aya Alasmar, Anas Hamad, Shereen Elazzazy	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019
Ifosfamide-Induced Encephalopathy: A Rare but Fatal Outcome	Amaal Gulied, Hebatalla Afifi, Shereen ELazzazy, Anas Hamad	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019
Evaluation of Ribociclib Use in the National Center for Cancer Care and Research: Retrospective Cohort Study	Farah Jibril, Shereen Elazzazy	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019.

Title	Research team	Conference
Perceptions and Expectations of Health Care Providers towards Clinical Pharmacy Services at the Tertiary Cancer Center in Qatar	Nabil H. Omar, Abdulqadir J Nashwan Yassin Eltorki, Oraib Abdallah, Hebatalla Afifi, Nancy Kassem, Mohamed Yassin, Shereen Amin El Azzazy, Anas Hamad	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019.
The Impact of New Gyn-Oncology Cancer Treatments in Qatar: Medication Use Evaluation (MUE)	Shereen Elazzazy, Hebatallah Afifi, Arwa Sahal, Amaal Gulied, Farah Jibril, Nabil Omar, Aya Alasmar, Anas Hamad	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019
Barriers and Trends in Cancer Patients` Pain Management in Qatar: A Randomized Cohort Prospective Study	Rehab Abdelwahab, Anas Hamad, Randa Al Okka,Mohd A Wahid, Khalil Ullah Shibli, Wael Saleem, Ahmed El Geziry, Fathi Saleh, Kakil Rasul, Shereen Elazzazy	The 5th Qatar International Pharmacy Conference (QIPC), Doha, Qatar, 6-8th Feb. 2019.
2nd Doha-Heidelberg Research Conference and Rare Disease Symposium, Doha, Qatar 7th-8th February 2019		
Targeting of Jak/Stat signaling pathway in multiple myeloma cell lines	Sabah Akhtar, Shilpa Kuttikrishnan, Siveen K. Sivaraman, Kirti S. Prabhu, Abdul Quaiyoom Khan, Maysaloun Merhi, Ruba Taha, Halima El Omri, Said Dermime, Shahab Uddin	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Intraosseous Lipoma: a challenging diagnosis.	Sameera Rashid	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Constructing a Model of Care for Post-Operative Breast Cancer Related Lymphedema and Functional Impairments in Qatar	Mohamed Shafi, Emad Abdalla, Ai Tanimizui Noora Rashid Al-Mudahka	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Tumor-Associated Pruritus: Interleukin-31 Induces Itch in Patients with TH2-Mediated Diseases Including Mycosis fungoides and Sezary Syndrome	Joerg Buddenkotte, Michael Kulinski, Said Dermine, Roopesh Krishnankutty, Ferda Cevikbas, Alexander Knuth, and Martin Steinhoff	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019

Title	Research team	Conference
Accuracy of Screening Mammography Interpretation by Characteristics of Radiologists: Jordanian prospective	Mohammad Rawashdeh	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Treatment with 5-Aza-2′-deoxycytidine in non-small cell lung cancer cells upregulate the NY-ESO-1 cancer-testis antigen expression, initiate apoptosis but down regulate cell growth and cell proliferation	Varghese Inchakalody, Shereena Sherif, Sara Taleb, Vidhya Sadhasivan Pasdaran, Asma A. El-Ashi, Roopesh Krishnankutty, Sivaraman SK, Abdul Quaiyoom Khan, Fouad Azizi, Mohammed Sahir Fairooz Panayampilly, Queenie Fernandes ,Lobna Al-Zaidan, Ahmed Iskandarani, Lubna Therachiyil, Afsheen Raza, Maysaloun Merhi, Shehab Uddin, Eyad Elkord, Said Dermime	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
A patient with gastric adenocarcinoma cancer responding to combined radiotherapy/ pembrolizumab (anti-PD-1) treatment demonstrates strong increase in T cells response against the NY-ESO-1 antigen	Maysaloun Merhi, Afsheen Raza, Varghese Philipose Inchakalody, Niloofar Allahverdi, Munir Jalis, Mohamed Sir Elkhatim Hamid, Mai Mostafa, Abdul Rehman Zar Gul, Shahab Uddin and Said Dermime	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Evaluation of Knowledge, Attitudes, and Practices of Skin Cancer among the Residents of Pokhara Valley, Nepal	Mohammad Asim, Brijesh Sathian, Ahammed Mekkodathil	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Malignancy in giant cell tumor of bone: A case of rapid transformation in an unprecedented site	Orwa Elaiwy	Doha-Heidelberg research Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Novel genetics findings by clinical exome sequencing in highly consanguineous Middle Eastern families with suspected Mendelian disorder from Qatar	Nader Al-dewik, Howida Mohd, Mariam Al-mureikhi, Rehab Ali, Fatma Al-mesaifri, Laila Mahmoud, Noora Shahbeck, Karen El Akouri, Mariam Almulla, Reem Al Sulaiman, Sara Musa, Gabriele Richard, Jane Juusola, Fowzan ALkuraya, Tawfeg Ben-Omran	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019

Title	Research team	Conference
Evaluation of Trabectedin Safety and Effectiveness at a Tertiary Cancer Center in Qatar: A Retrospective Analysis	Nabil Omar	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Identifying Lynch syndrome in two families with classical hereditary breast and ovarian cancer syndrome phenotype: A case report	Salha Bujassoum, Reem Alsulaiman, Hind Elmalik, Kulssom Junejo, Ahmed Mahfouz, Hanan Farghaly	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Cancer genetics in Qatar: Data on common and rare cancer syndromes	Reem Alsulaiman, Salha Bujassoum, Hekmet Bugrein, Tawfeg Ben Omran, Fatemeh Abbaszadeh, Nawal Bakheet, Sitti Apsa Kusasi, Nema Abdou, Benjamin Solomon, Hefedh Ghazouani	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Primary Leiomyosarcoma of Bone, Rare Entity and Challenging Diagnosis	Dr.Khaled Al-Sawalmeh, Dr.Adham Ammar, Dr. Ahmed Mounir El Sayed	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Cellular Angiofibroma: Unusual presentation	Dr. Hayan Abo Samra, Dr. Adham Ammar	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Towards Precision Medicine in Blood Cancers Genomic profiling of myeloid malignancies for the clinical setting	Susanna Akiki	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Chronic Myeloid Leukemia (CML) is a common hematological malignancy with tyrosine kinase inhibitors (TKIs) forming the main stay of treatment.	Shafaq Maqsood, Shaukat Khanum, Usman Ahmad, Umme Kalsoom Awan	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Pulmonary Mucoepidermoid Carcinoma: Diagnosis and Treatment	Shafaq Maqsood, Shaukat Khanum, Usman Ahmad, Umme Kalsoom Awan	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019

Title	Research team	Conference
Clinical outcome of stereotactic radiosurgery versus stereotactic radiotherapy in the management of intracranial meningioma: a systematic review and meta-analysis.	Nida Fatima	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Melanocytoma of the cerebellopontine angle associated with ipsilateral oculodermal melanosis: A rare tumor with unique association	Khaled Murshed, Abdulrazzaq Haider	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Subcutaneous Nematode mimicking a soft tissue neoplasm: A case report	Khaled Murshed, Rayan Sibira, Adham Ammar	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Testicular Sclerosing Sertoli Cell Tumor	Kamran Bhatti, Nadeem Sohail	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Masquerade as malignancy; Urinary bladder's recurrent and progressive disease	Kamran Bhatti, Nadeem Sohail, Faaz Gomah	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Fibrous pseudo tumor of para testicular region	Kamran Bhatti, Nadeem Sohail	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Predictors of breast self - examination awareness among the residents of Nepal	Brijesh Sathian, Mohammad Asim, Ahammed Mekkodathil, Supram Hosuru Subramanya, Arnab Ghosh	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
Sorefinib/Anti-PD-1 (Nivolumab) treatment and high-grade hepatocellular carcinoma-a case report on the role of Melanoma associated antigen (MAGE)-A3 as a potential biomarker of response	Afsheen Raza, Maysaloun Merhi, Varghese Philipose Inchakalody , Queenie Fernandes,Niloofar Allahverdi , Munir Jalis, Shereena Sherif , Juby Sara Koshy, Kakil Ibrahim Rasul, Mohamed Sir El Khatem, Arwa Essam Eldeen, Mai Mostafa, Abdul Rehman Zar Gul , Jonas Fielchenfield , Shahab Uddin and Said Dermime	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019

Title	Research team	Conference
Clinical Benefit of Trastuzumab in Metastatic HER2-Positive Gallbladder Carcinoma Report of 2 cases	A Ahmed, Farah Jibril, Adham Ammar, Ahmad Mahfouz, Lajoz Szabados, Gianfranco Pittari, Al-Hareth Al-Khater, Kakil Rasul, Jonas Feilchenfeldt	Doha-Heidelberg research conference 2019, Doha, Qatar 7th-8th February 2019
16th World Hematology Congress, Rome, Italy March 18th-19th, 2019		
Intramural great vessel lymphoma presenting as a thrombus in an aortic aneurysm	Shehab F Mohamed, Sameera Rashid , Mohamed A Yassin, Laith Tbishat, Abdulqadir J. Nashwan, Hassan Althani, Issam A Al-Bozom	16th World Hematology Congress, March 18th -19th, 2019 at Rome, Italy
Rituximab twice weekly for refractory thrombotic thrombocytopenic purpura in a critically ill patient with ARDS	Shehab F Mohamed, Mohamed Abdelaty, Abdelraouf Akkari, Abdurrahman Ali Elbuzidi, Abdulqadir J. Nashwan, Firyal Ibrahim, Mohamed A Yassin	16th World Hematology Congress, March 18th -19th, 2019 at Rome, Italy
Paroxysmal Nocturnal Hemoglobinuria (PNH) and G6DP deficiency (two hemolytic anemias) on the same patient	Shehab F Mohamed, Firyal Ibrahim, Khalid Shariff Nagham Sadik, Abdulqadir J. Nashwan, Deena Sideeg Mudawi, Mohamed A Yassin	16th World Hematology Congress, March 18th -19th, 2019 at Rome, Italy
NCCN 2019, in Orlando, Florida, USA. 21st -23rd March 2019		
Barriers and Trends in Cancer Patients' referrals to Pain Management in Qatar: A Randomized Cohort Prospective Study	Rehab Abdelwahab, Anas Hamad, Khalil Ullah Shibli, Shereen Elazzazy, Randa Al Okka,Mohd A Wahid, Ahmed El Geziry, Fathi Saleh, Kakil Rasul, Wael Saleem	NCCN 2019, 21st-23rd March 2019 in Orlando, Florida, USA.
Evaluation of the use of a single dose rasburicase in prophylaxis and management of Tumor Lysis Syndrome (TLS) among cancer patients in Qatar	Nancy Kassem, Halima El Omri, Mohamed Yassin, Shereen Elazzazy	NCCN 2019, 21st-23rd March 2019 in Orlando, Florida, USA
European Congress of Neuroradiology, Antwerp, Belgium 3rd April 2019		

Title	Research team	Conference
SuprahyoidNeckImaging	Dr Salman Qureshi	European Congress of Neuroradiology, Antwerp, Belgium, 3rd April 2019
29th European Congress of Clinical Microbiology and Infectious Disease (ECCMID) Congress, Netherlands 13th -16th April 2019		
TPN calculations	Shereen Elazzazy	Corporate HMC dietitians, April 10th, 2019, Ibn Nafis auditorium, Doha, Qatar
TPN concepts and guidelines	Shereen Elazzazy	Corporate HMC dietitians, April 10th, 2019, Ibn Nafis auditorium, Doha, Qatar
Cerebral schistosomiasis: case series from Qatar	Ahmed Zaqout, Fatma Ben Abid, Khaled Murshed, Issam Al-Bozom, Ghaya Al-Rumaihi, Hussam Al Soub, Muna Al Maslamani, Abdullatif Al Khal	29th European Congress of Clinical Microbiology and Infectious Disease (ECCMID) Congress, Netherlands13-16 April 2019
The Society for Pediatric Radiology 2019 Annual meeting San Francisco 30th April to 4th May, 2019		
Mimicker or a sinister lesion- inflammatory myeofibroblastic tumor, a diagnostic enigma unveiled	Sreekumar Muthiyal, Vishwanatha Kini, Shieja Mary Koshy	The Society for Pediatric Radiology 2019, Annual Meeting and Post-graduate Course. Hilton, San Francisco Union Square, San Francisco. 30th April to 4th May 2019
21st Annual European Pharma Congress Zurich, Switzerland May 20th-22nd , 2019		
The role of the pharmacist in decreasing discharge medication discrepancies: A prospective observational study	Taghrid Shehteh Abu Hassan, Sumaya Al Yafei, Radwa M Hussein, Sahar Nasser, Ahmed Basha, Hafedh Ghazouani and Shereen Elazzazy	21st Annual European Pharma Congress Zurich, Switzerland May 20-22, 2019

Title	Research team	Conference
MASCC/ISOO 2019, in San Francisco, California, USA 21st-23rd June, 2019		
Barriers and Trends in Cancer Patients' referrals to Pain Management in Qatar: A Randomized Cohort Prospective Study	Rehab Abdelwahab, Anas Hamad, Khalil Ullah Shibli, Shereen Elazzazy, Randa Al Okka,Mohd A Wahid, Ahmed El Geziry, Fathi Saleh, Kakil Rasul, Wael Saleem	MASCC/ISOO 2019, 21st -23rd June 2019 in San Francisco, California, USA
prophylaxis and management of tumor lysis syndrome (TLS) amongst cancer patients in Qatar: a retrospective cohort study	Nancy Kassem, Halima El Omri, Mohamed Yassin, Shereen Elazzazy	MASCC/ISOO 2019, 21st -23rd June 2019 in San Francisco, California, USA
European Society for Pediatric Endocrinology, Vienna, Austria 19th -21st September		
Effects of Iron Therapy on Pituitary Gonadal Axis and Sperm Parameters in Adults with Iron Deficiency Anemia (IDA)	Ashraf T Soliman, Mohamed A Yassin, Mohamed O Abdelrahman	European Society for Pediatric Endocrinology, 19th -21st September in Vienna, Austria
European Society of Neuroradiology, Oslo, Norway 20th Sep 2019		
CPA / IAM tumours / hearing loss	Dr Salman Qureshi	European Society of Neuroradiology, Oslo, Norway, 20th Sep 2019
ESMO Congress 2019, Barcelona, Spain 27th September – 1st October 2019		
A Phase I Clinical Trial of Malignant Pleural Mesothelioma Treated with Locally Delivered Autologous Anti-Fap-Targeted Car T-Cells	Alessandro Curioni[1] ,Christian Britschgi[1], Stefanie.Hiltbrunner2, Lorenz Bankel3, Pratishka Gulati[4], Walter Weder[5], Isabelle Opitz[5], Olivia Lauk[5], Claudia Caviezel[5], Alexander Knuth[6], Christian Münz[7], Christoph Renner[8], Rolf A.Stahel[9], Ulf Petrausch[10]	ESMO Congress 2019, 27th Sep – 1st Oct 2019, Barcelona, Spain
European Society Head & Neck Radiology, Palermo, Italy 4th Oct 2019		

Title	Research team	Conference
Cerebellopontineangletumours	Dr Salman Qureshi	European Society Head & Neck Radiology, Palermo, Italy 4th Oct 2019
The XVIII International Symposium on Oncology Pharmacy Practice (ISOPP 2019), London, United Kingdom October 10th - 13th, 2019		
Perceptions and Expectations of Health Care Providers towards Clinical Pharmacy Services at a Tertiary Cancer Center in Qatar	Nabil H. Omar, Shereen Amin El Azzazy, Abdulqadir J Nashwan Yassin Eltorki, Oraib Abdallah, Hebatalla Afifi, Nancy Kassem, Mohamed Yassin, Anas Hamad	The XVIII International Symposium on Oncology Pharmacy Practice (ISOPP 2019), London, United Kingdom October 10th - 13th , 2019.
The 1st Qatar Immuno-Oncology Summit (1st QIOS), Muscat, Oman November 2nd, 2019		
The management of Immunotherapy irAEs	Shereen Elazzazy	the 1st Qatar Immuno-Oncology Summit (1st QIOS), Muscat, Oman, November 2nd, 2019
ASH 2019, Orlando, Florida December 06th - 10th, 2019		
Evaluation of Pulmonary Function in Patient with Transfusion Dependent Beta Thalassemia with Severe Iron Overload	Mohamed A Yassin, Mushtaq Ahmad, Shehab Mohamed, Khadra S Yassin, Abdulqadir Jeprel Nashwan, Vincenzo Desanctis, Ashraf Tawfiq Soliman	ASH 2019, December 06th - 10th, 2019, Orlando, Florida
ESMO Immuno-Oncology, Geneva, Switzerland 12 Dec 2019		
Identification of a novel promiscuous anti-NY-ESO-1 immunogenic CD4+ peptide containing a CD8+ T-cell epitope highly present in metastatic gastric cancer responding to combined radiotherapy/anti-PD-1 immunotherapy	Said Dermime, Maysaloun Merhi	ESMO Immuno-Oncology
5-AZA treatment induces cytotoxicity and in vitro expression of immunogenic NY-ESO-1 antigen in non-small lung cancer cell NCI-H1975.	Varghese Inchakalody	ESMO Immuno-Oncology

Active Research Projects

Study Title	Principal Investigator	Funding Body
A Study of 18F-FLT Positron Emission Tomography (PET)/Computed Tomography imaging in cases of Profibrotic/Early Primary Myelofibrosis (PMF) and Essential Thrombocythemia (ET).	Mohamed Yassin	MRC/HMC
Epidemiologic and Clinical Characteristics Of Malignant Lymphoma In Qatar, 2013-2017: A Population-Based Cohort	Mr. Ahmad Mohammad Adel El Sayed	MRC/HMC
breast cancer in the elderly our experience in Qatar	Dr. Salman Husain Alshaibani	MRC/HMC
The Impact of Ethnicity on the Response to Eltrombopag in Patients with Immune Thrombocytopenia (ITP) in Qatar: A Single Institution Experience	Dr. Mohd. Abdeldaem Mohd. Yassin	MRC/HMC
Effects of Fasting on Patients with Immune Thrombocytopenia (ITP) Receiving Eltrombopag	Dr. Mohd. Abdeldaem Mohd. Yassin	MRC/HMC
Therapy related Myeloid neoplasms: Clinical and Pathologic Perspectives.	Dr. Dina Sameh Abdelrahman Soliman	MRC/HMC
Cost?Effectiveness Analysis of the Use of Ribociclib Versus Palbociclib for Hormone? Receptor?Positive and HER2? Negative Stage?IV Breast Cancer in Qatar	Ms. Shereen Amin Mahmoud Elazzazy	MRC/HMC
Dasatinib And Nilotinib As Upfront Therapy for Chronic-Phase Chronic Myeloid Leukemia (CML-CP) In Qatar: A Cost Effectiveness Analysis	Mr. Ahmad Mohammad Adel El Sayed	MRC/HMC
Relationship between Communication and Health-Related Quality of Life in Cancer Patients in Qatar	Ms. Sahar Saadani A Maksoud	MRC/HMC
The Association Between the Use of Diuretics and the Risk of Skin Cancer In Qatar: A Retrospective Cohort Stud	Ms. Fatima Abdulla A B Almaraghi	MRC/HMC
Highly aggressive CD4-positive Mast cell leukaemia(leukaemic variant) associated with isolated trisomy 19 and hemophagocytosis by neoplastic mast cells- a diagnostic experience and review	Dr. Dina Sameh Abdelrahman Soliman	MRC/HMC

Study Title	Principal Investigator	Funding Body
Re treatment using cetuximab and chemotherapy in patient with metastatic colorectal ca harboring wild RAS gene	Dr. Kakil Ibrahim Rasul	MRC/HMC
Autoimmune Hemolytic Anemia after Relapse of Chronic Myeloid Leukemia: A Case Report	Dr. Tahseen Hamamyh	MRC/HMC
High-Grade Basal Cell Adenocarcinoma of Sino-nasal Cavity of Minor Salivary Gland with weak PD-L1 positivity.	Dr. Aladdin I-M-Kanbour	MRC/HMC
Hyper progression to Nivolumab in SMARCA4 deficient tumor. Case report	Dr. Mohamed Sir Elkhatim Hamid Mohamed Ahmed	MRC/HMC
A rare case of copper deficiency in an infant with exclusive breast feeding mimicking MDS	Dr. Samah Ahmed Samy Aly Kohla	MRC/HMC
Case Series of immunotherapy in patients with colorectal Cancer and DNA mismatch repair defects. Cancer and DNA mismatch repair defects	Dr. Kakil Ibrahim Rasul	MRC/HMC
Composite Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Mantle Cell Lymphoma; small cell variant: A real diagnostic challenge. Case presentation and review of literature	Dr. Feryal Abbas Ibrahim Hilmi	MRC/HMC
Triple Negative Breast Cancer Prospective Registry in Eastern Europe, Middle East and Africa.	Salha Bujassoum Al Bader	MSD
A Phase III Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 in Combination with Tremelimumab Therapy Versus Standard of Care Platinum-Based Chemotherapy in First Line Treatment of Patients with Advanced or Metastatic Non-Small-Cell Lung Cancer (NSCLC).	Kakil Rasul	AstraZeneca
A Phase IV observational study in Chronic Immune Thrombocytopenia patients on Revolade® treatment in emerging markets.	Mohamed Yassin	Novartis

Study Title	Principal Investigator	Funding Body
A Randomized, Multicenter, Open-Label Cross-Over Study to Evaluate Patient Preference and Satisfaction of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab in Patients with Her2-Positive Early Breast Cancer.	Salha Bujassoum Al Bader	Roche
The role of immunoscore in solid tumors: a prognostic and predictive impact on patient outcomes	Mahmoud Gasim	MRC/HMC
Screening and Characterization of the Humoral and Cellular Immune Responses against the NY-ESO-1 Cancer Testis Antigen in Cancer Patients.	Afsheen Raza	MRC/HMC
Expression Profile of Lymphoid Enhancer binding Factor (LEF-1), a New Marker in Low Grade Lymphoma	Dina Soliman	MRC/HMC
Double-Hit and Double Expresser Lymphomas: A Clinicopathological Profiling of Large B-Cell Lymphomas in Qatar	Dina Soliman	MRC/HMC
Molecular Biomarkers in Hematologic Malignancies	Dina Soliman	MRC/HMC
Application of array based comparative genomic hybridization assay for the investigation of prognostic genomic alterations in chronic lymphocytic leukemia at diagnosis and during follow-up	Ruba Taha	Internal Research Grant MRC/HMC
Investigation of Anti-Tumor T-Cells Responses Generated In Vitro Against NY-ESO-1 Antigenic Protein Versus NY-ESO-1-Protein/ NY-ESO-1 -Antibody Immune Complex.	Maysaloun Merhi	MRC/HMC
Pilot study of dynamic biomarkers of response to anti PD1 immune check point inhibitors in head and neck squamous cell carcinoma patients	Said Dermime	MRC/HMC
Mapping Genotype to Phenotype for Colorectal Cancer Stem Cells: Implications and Perspectives in Cancer Therapy	Cristina Maccalli Mohamed Abu Nada Said DermimeW	QNRF/NPRP 10th Cycle

Study Title	Principal Investigator	Funding Body
Using DNA-Typing and Erythrocyte Micro-particle Analysis to Detect Blood Doping.	Sven Voss Mohamed Yassin	MRC/HMC
Precision Immunology Implications for Aggressive Types of Breast Cancer: Genomic Determinants of Immune Response to Neoadjuvant Chemotherapy	Salha Bujassoum Al Bader Lotfi Chouchane	MRC/HMC
Cancer testis antigens as candidate targets for cancer immunotherapy of triple negative breast cancer and the role of hypoxia in T-cell based immunotherapy.	Julie DeCock Said Dermime	QBRI Internal Grant
Investigation of immune cells in colorectal cancer	Eyad Elkord Mohamed Abu Nada	MRC/HMC
Screening Protocol for Genetic Diseases of Immune Dysregulation and Autoimmunity	Afraa Suliman	No Funding
Developing a vaccine against MERS in camels.	Said Dermime Martin Bachmann	Internal Research Grant MRC/HMC
Development and exploration of a novel personalized breast-cancer vaccine based on virus-like particles by incorporating tumor-specific T-cell epitopes	Mona Mohsen Said Dermime	PEDRA award 4th Cycle/QNRF
Whole Genome Sequencing for Myeloproliferative Neoplasms (MPNs) revealing the Genetic Background of Arabs in Qatar: Revisiting the Pathogenesis.	Mohamed Yassin	MRC/HMC

Educational Activities

Visiting Speakers and Guest Lectures

There was a total of 34 lectures presented in NCCCR and iTRI in 2019. These lectures were delivered by HMC physicians, local academic partners and representatives from other organizations from Qatar and worldwide.

Date	Title of presentation	Speaker
23-January-19	Acute Myeloid Leukemia	Prof Christian Thiese, BioScreening Technology Group Manager at the University of Leeds
20-February-19	"From bone marrow transplantation to novel cellular therapies- A paradigm shift in modern haemopoeitic stem cell transplant programme"	Dr Muhammad Saif- Guest Speaker, Director of Stem Cell Laboratory in Manchester University Hospital
24-February-19	CLL Lecture	Prof John Seymor, Associate Director of Clinical Research at the Peter MacCallum Centre, Cancer Centre in Melbourne, Australia.
25-February-19	'Rectal cancer organ preservation: Intensification of chemoradiation using novel agents and other strategies.'	Dr Simon Gollins, Clinical Oncologist, Christie Hospital Manchester, UK
10-March-19	Overview on BTKi in B-cell NHL	Dr Eric Jacobsen, Sheldon Emery Professor of Chemistry and Chair of the Department of Chemistry and Chemical Biology at Harvard University
18-March-19	"Managing Fungal Infection in Hematological Setting"	Dr Samir Agrawal- Consultant Haemato-Oncologist at St Bartholomew's Hospitals and The Barts Health NHS Trust, London UK.
9-April-19	Management of Multiple Myeloma Patients	Prof. Mohamed Mohty, Professor of Hematology and Head of the Hematology and cellular therapy Department at the Saint-Antoine Hospital and Sorbonne University (Paris, France)

Date	Title of presentation	Speaker
14-April-19	"Germline genetics of hematological malignancies, focus on myeloma"	Dr. Kari Hemminki- Head Division Molecular Genetic Epidemiology, DKFZ.
16-April-19	Update on Management of Non-Small Cell Lung Cancer	Dr Mark Vincent- Medical Oncologist in London Regional Cancer Program.
17-April-19	Non-Surgical Local Treatment Strategies for Colorectal Liver Mets	Dr. Alaaeldin Shiblak, Consultant Medical Oncology Southampton and Salisbury District Hospital,UK
23-April-19	'Rectal cancer organ preservation: Intensification of chemoradiation using novel agents and other strategies.'	Dr Simon Gollins, Clinical Oncologist, Christie Hospital Manchester, UK
1-May-19	"Updates on the use of Eltrombopag with patient with thrombocytopenia secondary to SAA as first line treatment option, data from last ASH 2018"	Dr. Phillip Scheinberg, Chief of Clinical Hematology at Hospital Sao Jose, Beneficencia Portuguesa de Sao Paolo
19-June-19	2016 Updates to the WHO Brain Tumor Classification System: What the radiologist Needs to Know	Dr. Surjrth Vattoth Senior Consultant Neurosciences Institute
19- June-19	Influence of Residual Disease Following Surgical Resection in Newly Diagnosed Gioblastoma on Clinical, Neurocognitive, and patient Reported outcomes	Dr. Rasha Elbadry
19- June-19	The Survival Effect of Repeat Surgery at Glioblastoma Recurrence and its Trends: a Systemic Review and Meta-Analysis	Dr Mohamed Alhoobi Medical Resident
19- June-19	REGOMA: a randomized, multicenter, controlled open-label phase II clinical trial evaluating Regorafenib activity in relapsed glioblastoma patients	Dr. Ashraf Awad Associate Consultant Oncology, NCCCR
19-June-19	Phase II Study of Radiation Therapy Plus low dose Temozolamide followed by Temozolamide and Irinotecan for Gioblastoma: NRG Oncology RTOG Trial 0420	Dr. Mohamed Reyaz Senior Consultant Radiation Oncology NCCCR

Date	Title of presentation	Speaker
24-June-19	Translational Applied Health Research: a tale of Anti- Cholinergic Burden (ACB)	Professor Phyo Kyaw Myint Chair in Old Age Medicine (Clinical), Inst. of Applied Health Sciences, University of Aberdeen
8-September-19	Recent updates in advanced breast cancer management	Dr Debasish Tripathy, Professor and Chairman, Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
15-September-19	Management of Hemophilia	Prof Johnny Mahlangu (Hematology Professor- University of Witwatersrand)
16-September-19	Optimizing treatment options in RAS wild-type mCRC patients	Dr. Scartozzi Mario, Prof- University of Cagliari
9-October-19	new strategies in Multiple Myeloma management	Prof. Thierry FACON- Professor of Haematology in the Department of Haematology, Lille University Hospital, Lille, France
13-October-19	Atopic Dermatitis and Nerve Growth Factor	Professor Hiroshi Matsuda (Professor, Division of Animal Life Science, Institute of Agricuture, Tokyo University of Agriculture and Technology)
20-October-19	Updates in management of Endometrial Cancer	Dr Rowan Miller, Consultant Medical Oncologist at University College London and St Bartholomew's Hospitals
21-October-19	Chronic Lymphocytic Leukemia	Dr. Imad Tabbara, Hematology Specialists at George Washington University Hospital
22-October-19	Updates in management of hormone receptor positive in breast CA	Mothaffar F. Rimawi, M.D. (Prof and Executive Medical Director of the Dan L Duncan Comprehensive Cancer Center (DLDCCC) at Baylor College of Medicine

Date	Title of presentation	Speaker
6-November-19	Pediatric Regimen for Adults with ALL	Prof Stephen Mackinnon, University College London, UK
11-November-19	Molecular Imaging and Thyroid Cancer. The New Clear Medicine	Dr. Mehdi Djekidel Division Chief and Lead for Nuclear Medicine and Molecular Imaging - Department of Diagnostic Imaging Sidra Medical and Research Center
17-November-19	Gestational Management Guidelines	Prof Michael Seckl Professor of Molecular Oncology and Director of the National Gestational Trophoblastic Disease, Imperial College Healthcare NHS
26-November-19	Care of patients with Immune-related toxicities	Dr. Sbeeh-ur-Rehman Butt, Visiting Consultant Fellow of Australasian College of Physicians of Australia (FRACP Medical Oncology)
1-December-19	Invasive Fungal Infection in patients with Immunogical Malignancies	Dr Honar Cherif, Assocaite Professor of Hematology - Uppsala University Hospital & Head of Dept. of Hematology Uppsala University
2-December-19	Updates in management of lung cancer	Dr. Rosario Campelo, Consultant Oncologist- Spain
3-December-19	Update in Benign Hematology	Dr Honar Cherif, Assocaite Professor of Hematology - Uppsala University Hospital & Head of Dept. of Hematology Uppsala University
9-December-19	21st Century Medicine: Personalized Medicine and Biomarker Discovery	Dr. Ali M. Ardekani, Mayhar Charity Institute, Tehran, Iran

Conferences and Workshops 2019

Date	Title	Organization Teams
12th January 2019	1st Doha Cardio Oncology Workshop	HMC - Heart Hospital and NCCCR
19th January 2019	Sarcoma Awareness.	HMC Sarcoma MDT, Qatar Cancer Society
25 -26th January 2019	2nd Doha Heidelberg Oncology Conference	HMC
15th -16th February 201	Engineered Immune Calls in Cancer Immunotherapy	Sidra Medicine, HMC, QCS.
5th - 6th April 2019	2nd Annual Qatar Hematology Symposium 2019 Myeloid	Hematology, NCCCR.
29th April 2019	2nd HOPE Conference	HMC NCCCR Pharmacy
29th -30 April	UK Qatar Health Research Forum "Joining Forces"	Qatar University - HMC AHS
19th-20th April 2019	Thyroid Cancer Conference	HMC Thyroid MDT, QCS
19th June 2019	1st Neuro-oncology Journal Club	HMC Neuro -Oncology MDT
31st August 2019	Guidelines for Suspected Cancer Referral Symposium.	MoPH PHCC QCS
21st September 2019	The 2nd Hematological Malignancies for Primary Care Symposium	QCS, HMC, NCCCR
28th September 2019	Guidelines for Suspected Cancer Referral Symposium.	MoPH PHCC QCS
17th -19th October 2019	Breast and Gynae Conferences	HMC Breast and Gynae Onc, MDT's
26th October 2019	The Art of Breast Cancer Care	CAN-Q, QCS, HMC
15th -17th November 2019	Gestational Trophoblastic Disease Symposium	HMC Gynae- Oncology MDT
24th-28th November 2019	Cancer Epidemiology: Methods and Analysis	MoPH
7th-8th December 2019	9th Annual Meeting: Middle Eastern Assoc. for Cancer Research	QU, QCS, MEACR
12th-14th December 2019	6th Colorectal Surgical and Oncology Combined Conference	HMC Dept. of Surgery, Colorectal Unit.
14th December 2019	The Medical Use of Internet in Cancer Care	CAN-Q, QCS, QU

Index of Researchers

A

Abdallah O 54

Abdelaal A 100, 124

Abdelfattah W 119

Abdelfattah K 94.95

Abdelrahman A 86

Abdelrahman A 100, 124

Abdelwahab R 141,143

Abdulla M 127

Abdulla MA 56

Abid FB 73,77

Abu Hassan T 64

Abu Jaber A 120

Abu Jarir R 86

Abu Nada M 27

Abuaqel S 61

Abushanab D 127

Abutaka A 81

Abu-Tineh M 88

Achkar I W 35,116

Adel A M 127

Adeli M 78

Adham A 93

Adham D 124

Afifi HM 54

Aftab Z 99

Afzal MZ 22

Agirre X 147,149

Agouni A 26

Ahmad M 137

Ahmed A 81

Ahmed EI 35, 37

Ahmed K 59

Ahmed S 122

Akhtar M 94,111-115

Akiki S 9,10,90

Akram J 100

Al Ansari A 118,77

Al Bozom I 61,73,83,84, 95,111,112,115

Al Dayel F 13

Al Fayea T 13

Al Hamad H 20

Al Husaini H 13

Al Hussain T 111

Al Kattan K 13

Al Khal A 73

Al Kuwari M 20

Al Maghrabi H 13

Al Malik H 113

Al Maslamani M 73

Al Nabet A 50,112, 113, 114

Al Okka, R 79, 141

Al Rimawi Y 74

Al Saadi W 133

Al Soub H 73

Al Sulaiman RJ 50, 74

Al Yafei S 64

Al Zaidan L 129, 135

Alali FQ 24

Alateeq L 100

AL-Azzazy S 96

Albader S B 74

AlBattah A 79

Al-Darwish MS 40

Al-Dewik N 29, 50,122

Al-Dhaheri M 27

Al-Hassan MS 124

Alhijji I 79

Ali R 50

Ali S M 99

Ali TA 24

Alignani D 147, 149

Al-Kowari M 61

Alkubaisi A 83

Alkuraya F 50

Allahverdi N 129

Al-Mesaifri F 50

Al-Muftah M 61

Almuhannadi H 20

Almulla M 50

Al-Mureikhi M 50

Al-Nabet A 50, 112, 113, 114,

Al-Naemi HA 116

Alobaidi M 20

Alobaidly A 77

Al-Okka R 79
Al-Rumaihi G 73
AlRumaihi K 61, 118
Alsaadi WA 52
Al-Sabbagh A 97
Alsaud A 88
Al-Shibani F 20
AlSulaiti E 20
Al-Tarakji M 99
Al-Thani H 79
Alvarez M. G 147
Alves Faustino Paiva B 148
Al-Zaidan L S 135
Alzubaidi R 118
Amundarain, A 149
Arredouani A 39
Ashi E AA 135
Ashour A 88
Atanackovic D 71
Atrott K 69
Ayakannu T 33
Azizi F 39, 106
Azouz R 122
Azrieh B 88
Azzaz, S 142

B

Babu S 77
Bachmann MF 11, 18, 108
Bahbah E 122
Bamefleh H 13
Bankel L 131
Barfield R 79
Bari M 33
Basha A 64
Bashir K 91
Becker E 69
Bedognetti D 31
Belkhair S 83
Ben Abid F 73, 77
Ben-Gashir M 94 ,100
Bengs S 69
Benjamin S 50, 145
Ben-Omran T 29, 50
Bernhard H 71
Bernstein L 122
Bhat AA 116
Blom HJ 29
Boehmer L 69, 71
Borghaei H 22
Borrow J 9, 10
Bouaouina N 31
Boujassoum S 31
Bounedjar A 13
Bretones G 147
Britschgi C 131
Britzen-Laurent N 69
Brzežniakiewicz-Janus K 46
Buddenkotte J 16
Burgos L 147
Busenhart P 69
Bylund CL 52

C

Cabral-Miranda G 11, 18
Calasanz MJ 147, 149
Carrasco-Leon A 149
Castro-Labrador L 149
Caviezel C 131
Chandran M 20
Chemale Y 62
Chen X 22
Chikri M 39
Chouchane A 31
Chouchane L 31, 61
Christner M 77
Christoph J 69
Coimbra F 62
Constantinescu G 62
Cosgarea I 62
Crestani V 62
Croner RS 69
Curioni A 131

D

Dabbous Z 145
Darweesh A 124
Dawoud RA 96
Oliveira JA 187
De Sanctis V 56,87

Index of Researchers

Del Orbe R 147
Derbala M 15
Dermime S 18,22,24,35-39,44,106,129,135
Desanctis V 137
Dhawan A 62
Driscoll T 78
Dyer SA 9,10

E

Eisa M S 89
El Beltagi AH 119
El Geziry A 141,143
El Hayek S 122
El Moghazy W 58
El Omri H 90,97,139,146-149
Elaffandi A 58
Elaiwy O 114
El-Akiki S 90
El-Akouri K 50
El-Ansari W 58,59,124
Elareer NR 24,109
Elazzazy S 54,64,79,96,139,143,146
El-Elimat T 24
Elhadd T 145
Elkhetim MS 121,129
Elkord E 27,135
Elmalik H 96
El-Matbouly M 81
Elmesery A 91
Elmoghazy W 58,59,81
Elmoheen A 91
Elorrabi M 20
Elsabah HM 35
Elsayed AM 95
Elsotouhy AH 20,119
Eltawagny M 91
Eltorki Y 54
El-Turabi A 11,18
Engeroff P 11
Ezponda T 149

F

Fadlelseid A 133
Fadul A 95
Fahem S 13
Fahmey A 122
Farfar K 92
Farghaly H 74
Feilchenfeldt J 129
Fernandes Q 135
Fernandes T 62
Filali T 13
Flores-Montero J 147
Fotin Mleczek M 71
Frankow M 46
Frantz R 26
Frei P 69
Fried M 69

G

Gabbouj S 31
Gad H 20
Gameil A 97
Garate L 149
Garate S 147
Garces JJ 147
Gawhale PV 20
Gerber B 42
Ghasoub R 79
Ghazouani H 64,121,133
Giacomo VD 29
Gil L 46
Gnad Vogt U 71
Goicoechea I 147
Gomes AC 18
Green F 145
Griffiths MJ 9,10
Grivel JC 105
Groschel A 71
Guimaraes P 62
Gulati P 131
Gunduz M 62
Gupta S 29
Guruceaga E 149

H

Haberle J 29
Haddad R 83
Haider A 83,113

Haight A 78
Halama M 69
Hamad A 141,143
Hamamyh T 85
Hammouda A 100
Haris M 105,116
Hashem S 116
Hashim L 50
Hassoun S 145
Heath MD 11
Helmi F 90
Helmy I 81
Hiltbrunner S 131
Hochwald S 22
Hoerr I 71
Hofman P 22
Hong HS 71
Hruz P 69
Hussein ML 102
Hussein RM 64
Hyassat S 114
Hydrose S 129

I

Ibrahim F 89,97
Inchakalody VP 129,135
Iskandarani A 24,135
Ismail HM 29

J

Jaafar H 13
Jalis M 129
Jaloudi M 13
Janahi IA 39
Jazieh AR 13
Jboor DH 40
Jenkins G 69
Jerobin J 35
Jimenez L 105
Jochebeth A 24
Johar D 122
Junejo K 109
Juusola J 50

K

Kallen K 71
Kamel Y 59
Kanbour A 74
Kasper S 69
Kassem N 54,139,146
Khalaf H 58,59,81
Khan AQ 35,37,44,106,109,135
Khawar M 27
Knuth A 11,18,42,69,71,108,131
Koch SD 71
Konje JC 33
Kramer MF 11
Krishnamoorthy N 29
Krishnankutty AR 16,135
Kruger WD 29
Kulinski M 16
Kundig TM 11,18
Kurtzberg J 78
Kuttikrishnan S 24,35,7,44,106,135

L

Lance MD 46
Lander T 71
Lang S 69
Larbaoui B 13
Lauk O 131
Lengyel Z 74
Leo R 16
Leonardo L 62
Lopez-Otin C 147
Lv T

M

Ma X 31
Maacha S 105
Maccarrone M 33
Machado F 62
Mahfoud ZR 20
Makinen MJ 69
Malik RA 20
Maliyakkal A 92
Mamie C 69
Manz MG 42
Martin P 78
Martinez-Lopez J 147

Index of Researchers

Mastrangelo N 33
Mateo JM 44,106
Mathew V 102
Mayer F 71
Mejia B 62
Mekhaimar M 124
Melikyan G 74
Merhi M 24,35-39,44,129,135
Mestiri S 129
Meydan C 149
Millacoy P 147
Mira RR 102
Miranda E 149
Mohamed G 99
Mohamed M 145
Mohamed NA 29
Mohamed SF 76,88-90,137
Mohammad RM 39
Mohd H 50
Mohsen MO 11,18,108
Mokrab Y 31
Mostafa M 129
Mottawea M 122
Mraiche F 44
Muelbe F 71
Mueller NJ 42
Muller J 18
Munusamy S 26
Munz C 131
Murner C M 42
Murshed KA 27,73,84,93-95
Musa S 50
Mustafa MH 121,122
Muth A 71

N

Nadukkandiyil N 20
Nair K 119
Nair VS 135
Naschberger E 69
Nashwan AJ 54,87-90,120,137
Nasrallah GK 29
Nasser SM 48,64
Naushad V 92
Nemir A 79
Nur U 40

O

Obeidat K 88
Oberlies NH 24
Olvera V 62
Omar NE 54,74,122,133
Opitz I 131
Ordonez R 149
Orfao A 147
Osman S 20
Own AM 20,119

P

Padmakumari A 87
Page K 78
Palomera L 147
Panayampilly SF 135
Parikh S 78
Parray AS 39
Pascual M 149
Pasha M 26
Pentz R 78
Perez A 147
Petkar M 15,121
Petrausch U 131
Petropoulos IN 20
Petrowsky H 69
Planes F 149
Ponirakis G 20
Prabhu KS 24,35-39,44,106
Prasad V 78
Probst J 71
Prosper F 147,149

R

Ramadan M 20
Rankin JM 52, 120
Raselli T 69
Rashid S 76,77,99,112-114
Rasul KI 13,59,74,106,121,141,143
Raza A 35,105,106,129,135

Raza A 86
Reck M 71
Rehman A 92
Relecom A 129
Remadi Y 31
Renner C 42,131
Richard G 50
Rickenbacher A 69
Riether C 11,18
Rios R 147
Rodriguez I 147
Rodriguez JJ 62
Rodriguez MJ 62
Rodriguez P 147
Roelands J 31
Roesti E 11
Rogler G 69
Ruedl C 18
Rupa-Matysek J 46

S

Saad M 31
Saaid L 99
Sadik N 89
Sahal A 48
Sahir F 35,135
Salatino S 18
Saleem W 141,143
Saleh F 141,143
Salman D 122
Samaras P 42
Sampedro Puente DA 147
Sande M 11
Sankaranarayanan A 20
San-Miguel JF 147,149
Sanoja-Flores L 147
Sayaman RW 31
Schanz U 42
Scharl M 42,69
Scheel B 71
Schellerer V 69
Schmidt A 42
Schneller F 71
Schonhaut L 62
Schroder A 71
Schwartz D 62
Sebastian M 71
Segura V 149
Seifert B 42
Shaaban A 86
Shaath N 92
Shah A 99,100
Shahbeck N 50
Shan J 31,61
Shanmugakonar M 116
Shariff K 89
Sheppard D 69
Sherif S 135
Shibli, K 141,143
Shuaib A 20
Sibira R 93
Sivaraman SK 16,26,129,135
Siveen KS 24,35,37,39,44,106
Skinner MA 11
Soliman AT 56,87,137
Soliman D 74,97
Solomon B 50
Song Y 22
Soofi M 81
Spalinger MR 69
Speiser DE 11,18,108
Stahel RA 131
Stein JV 11
Steinhoff M 16,24,35,37,39,106,109
Stenner-Liewen F 42
Stohlmacher J 71
Strack T 71
Sturzl M 69
Sulaiman R 50,74
Sulieman I 58,81
Sultan K 15

T

Taha NM 112,115
Taha R 35,44,79,149
Talaat M 121
Taleb S 135

Index of Researchers

Tamayo A 62
Taylor AH 33
Tbishat LF 76
Ternette N 18
Tfayli A 13
Therachiyil L 16,135
Thodi N 20
Thomas M 71
Thony B 29
Toor SM 27
Tosino R 20
Tukiendorf A 46
Tuomisto A 69
Turina M 69

U

Uddin S 16,24,35,39,44,105,106,109,116,135
Uppada S 116

V

Valcarcel L 149
Valdes-Mas R 147
Vattoth S 84,119
Vavricka SR 69
Vijay A 59
Vilas-Zornoza A 149
Vogel M 11,18

W

Wahid MA 141,143
Wan B 22
Weber A 69
Weder W 131
Wiegand V 71
Wolny-Rokicka E 46

X

Xu Y 22

Y

Yadav SK 116
Yassin A 118
Yassin KS 56,137
Yassin MA 54,56,76,85-90,95,97,127,139,146

Z

Zaqout A 73
Zar Gul A 121,129
Zawahreh A 120
Zayed H 29,35,106
Zeltins A 11
Zha L 11
Zhan P 22
Zhang T 22
Zhao Y 22
Zippelius A 71
Ziv E 31