Berliner Dialyse Seminar

Onco-Nephrology: An Emerging New Discipline

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DISCLOSURES

Potential conflicts of interest declaration

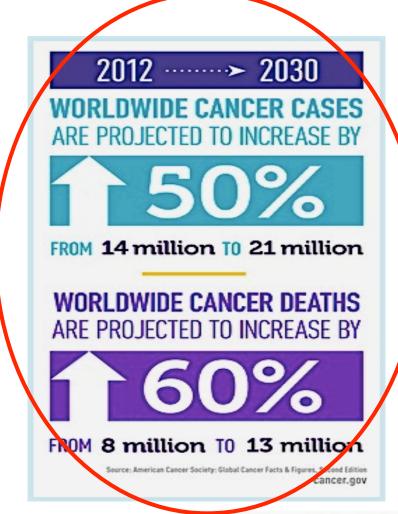
The content of the following speech is the result of efforts to achieve the maximum degree of impartiality and independence.

As a speaker, I hereby affirm that there are <u>no conflicts of interest</u> concerning the content of the following speech that are the result of employment, an advisory function or financial contributions for research projects, lectures or any other activity.

Cancer

A Common Global Problem

- Cancer is common and a leading cause of death worldwide
- Estimated 9.6 million deaths in 2018
- The most common causes of cancer death are the following:
 - LUNG (1.76 MILLION DEATHS)
 - COLORECTAL (862,000 DEATHS)
 - STOMACH (783,000 DEATHS)
 - LIVER (782,000 DEATHS)
 - BREAST (627,000 DEATHS)





The Kidney-Cancer Connection Onco-Nephrology

Electrolyte-Acid/Base Disorders

AKI

Anti-Cancer Drugs
Malignancy-related Kidney Injury
Radiation/Nephrectomy
Uremic Milleu (CKD, ESRD)

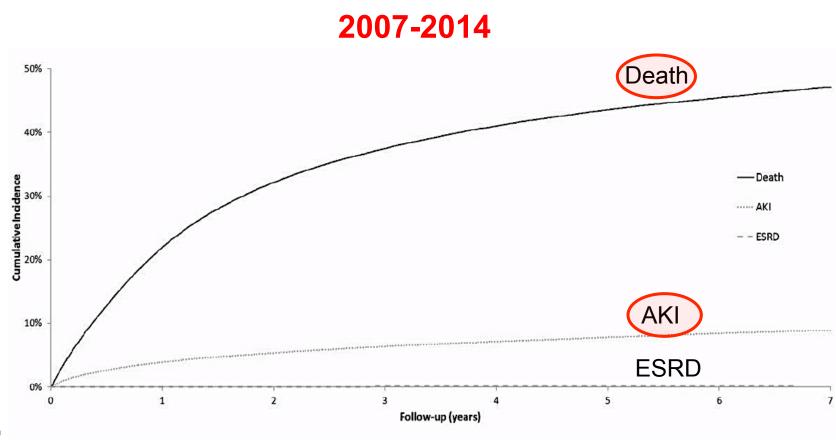
CKD

CANCER

AKI incidence

AKI is common among cancer patients

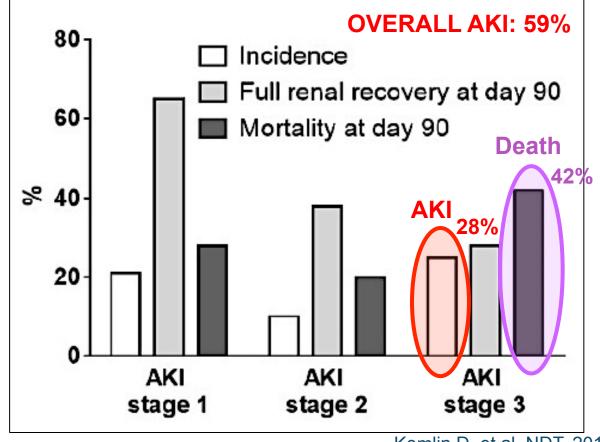
- Ontario, Canada: 163,071
 patients undergoing cancer
 therapy between 2007-2014
- One in 10 developed AKI-D or required hospitalization
- Annual incidence of AKI increased from 18 to 52 per 1000 person years
- Highest AKI incidence with myeloma (26%), bladder cancer (19%), leukemia (15%), and kidney cancer (14%)



AKI in Hospitalized ICU Patients

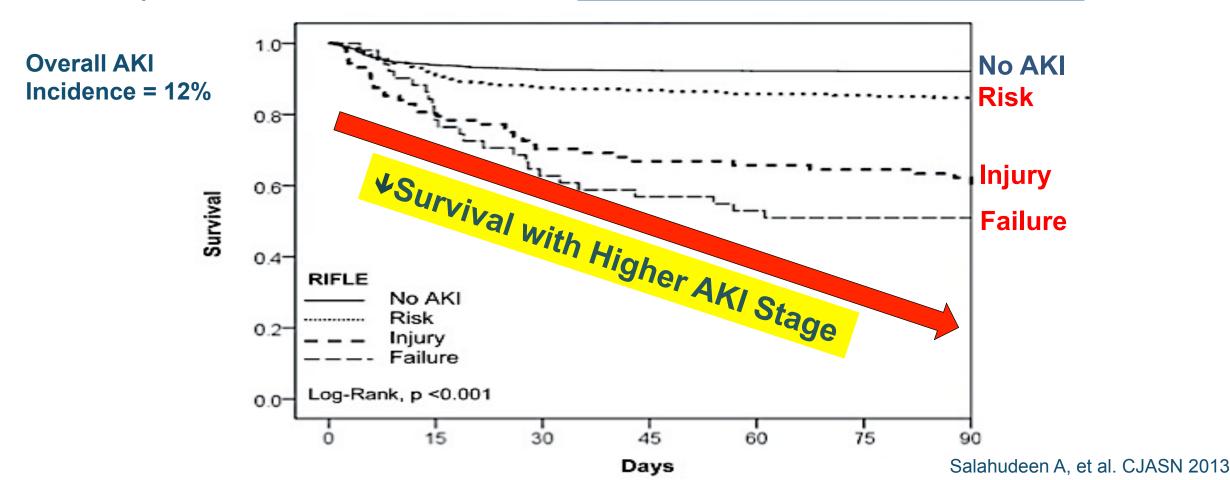
- Single center in France over 4 years
- Solid tumors admitted to the ICU (n=204)
- KDIGO AKI (59%) and mortality (37%) are common
- Sepsis, hypovolemia, and obstruction most common causes of AKI followed by TLS, hypercalcemia, and >1 etiology
- Stage 3 AKI (28%) with higher mortality (42%)

2011-2015



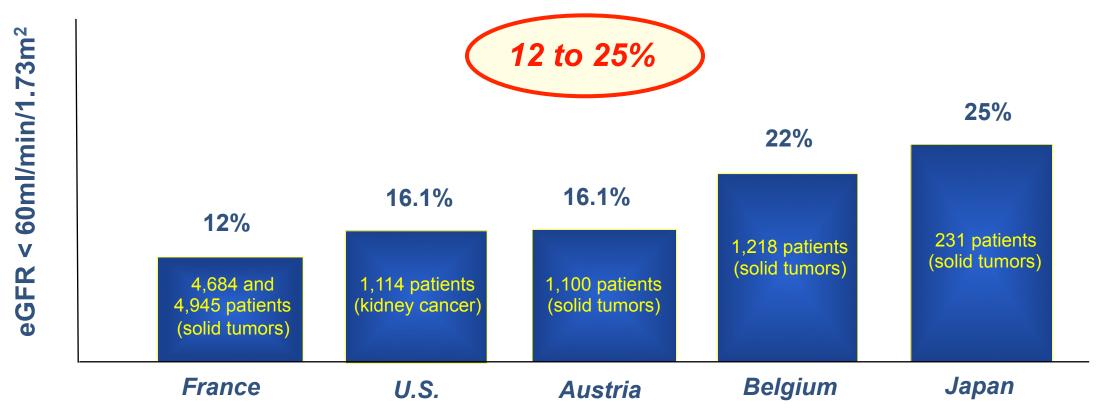
Increased Mortality with AKI

- Survival rates in cancer patients with AKI associated by RIFLE Criteria
- Kaplan-Meier survival curves—dose related reduction in survival



Chronic kidney disease in Cancer

 CKD (eGFR < 60 ml/min/1.73m²) is highly prevalent in cancer patients





Onco-Nephrology Increased Mortality with CKD

- CKD in cancer patients is associated with reduced survival
 - France: CKD stage 3 (eGFR < 60ml/min/1.73m²) HR 1.27 for Mortality
 - Australia: CKD stage 3 (eGFR < 60ml/min/1.73m²) HR 1.27 for Mortality
 - Korea: CKD stage 3 (eGFR 30 60ml/min/1.73m²) HR 1.12 for Mortality CKD stage 4 (eGFR < 30ml/min/1.73m²) HR 1.75 for Mortality
 - Japan: CKD stage 3 (eGFR < 60ml/min/1.73m²) is an independent risk factor for death at 1 year



Kidney Injury and Cancer

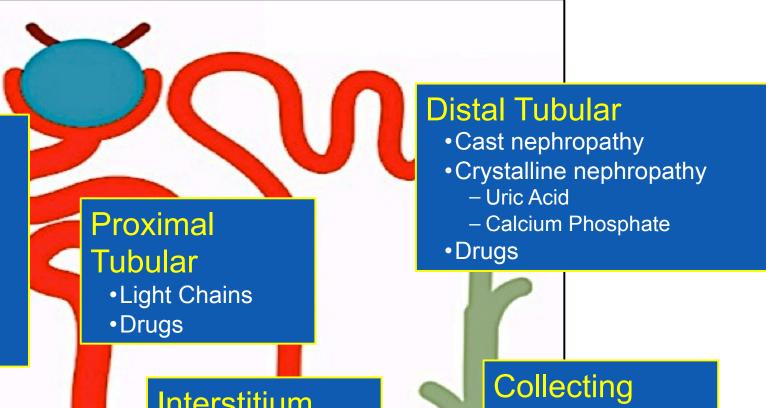
Sites of Kidney Injury

Vascular

- Hemodynamic
- •TMA
- Drugs

Glomerular

- •TMA
- MIDD/Amyloid
- Cryo GN
- PGNMID
- •C3GN
- •FGN/IT
- Drugs



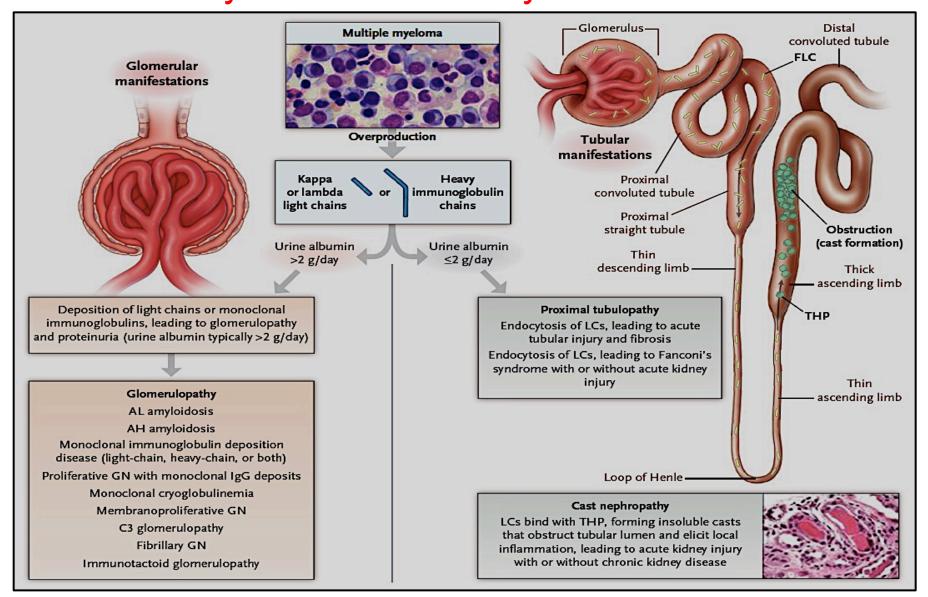
Interstitium

- Light Chains
- Drugs (AIN)
- •Lymphoma
- •Leukemia

System

- Lymphoma
- Leukemia
- Crystals
- Drugs

Onco-Nephrology Myeloma and Kidney Disease



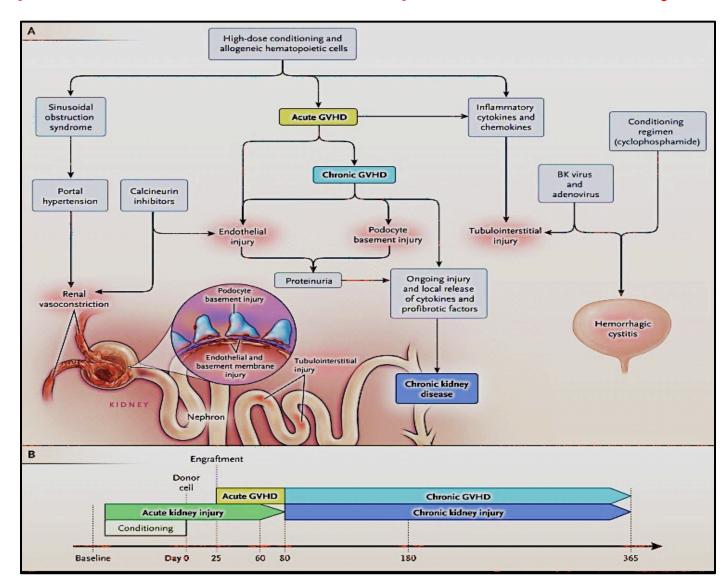
Onco-Nephrology Lymphoma/Leukemia and Kidney Disease

Acute Kidney Injury (AKI) in Patients With Leukemia or Lymphoma				
Cancer-Related AKI	Therapy-Related AKI			
Tumor infiltration of the kidneys (more common with lymphoma)	Therapy-related nephrotoxicity (including thrombotic microangiopathy, acute tubular injury, tubulointerstitial nephritis, intratubular obstruction, and glomerulonephritis)			
Retroperitoneal lymphadenopathy leading to urinary tract obstruction	Tumor lysis syndrome with acute uric acid nephropathy and/or acute nephrocalcinosis			
Hypercalcemia-related prerenal kidney injury	Nausea, vomiting, and diarrhea associated with prerenal azotemia			
Various paraneoplastic glomerular disorders	Sepsis-associated kidney injury			
Lysozymuria with acute tubular injury associated with AMoL or CMML (rare)	Nephrotoxicity (acute tubular injury and acute tubulointerstitial nephritis) from other common medications (NSAIDs, ACE inhibitors, ARBs, diuretics, antimicrobial agents)			
Acute tubulointerstitial nephritis associated with hemophagocytic disease (rare)	Contrast-associated kidney injury			
Disseminated intravascular coagulation (rare)				

Hematopoietic Stem Cell Transplant and Kidney Disease

AKI

- Chemotherapy
- SOS
- aTMA
- aGVHD
- Nephrotoxins
- Sepsis
- Drugs- AIN



CKD

- cTMA
- cGVHD
- Nephrotoxins
- Radiation
- Calcineurin Is
- Chemotherapy
- Drugs- CIN

Onco-Nephrology MGUS → MGRS

Defining MGRS for Hematologists/Oncologists and Nephrologists

- MGUS (plasma cells <10%, serum M protein <1 g/dL) that has kidney involvement
 - AKI, proteinuria, CKD
 - Various kidney lesions are described

Organized		ă	Nonorganized (granular)		
Crystals	Fibrillar	Microtubular		MIDD (Randall type)	Other
Myeloma cast nephropathy	Light chain amyloidosis	Type I and type II cryoglobulinemic glomerulonephritis		LCDD	Proliferative GN with monoclonal Ig deposits
Light chain proximal tubulopathy (with or without Fanconi syndrome)	Nonamyloid	Immunotactoid GN		LHCDD	Waldenström
Crystal-storing histocytosis	Fibrillary GN*	GOMMID		HCDD	Macroglobulinemia

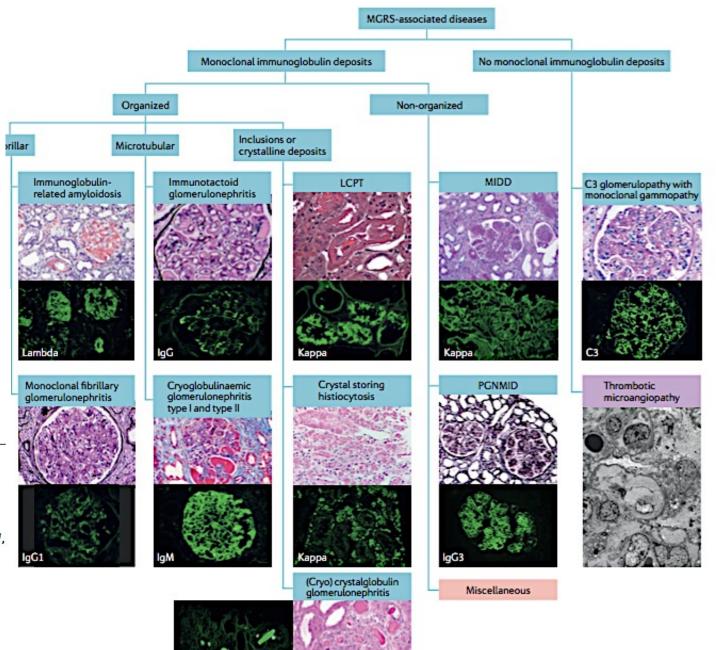
- Therapy initiated to reduce paraproteins
 - Prevent acute kidney injury (or help reverse AKI) and prevent development of future CKD

CONSENSUS

EXPERT CONSENSUS DOCUMENT

The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group

Nelson Leung *, Frank Bridoux², Vecihi Batuman³, Aristeidis Chaidos⁴, Paul Cockwell⁵, Vivette D. D'Agati⁶, Angela Dispenzieri¹, Fernando C. Fervenza¹, Jean-Paul Fermand⁻, Simon Gibbs⁶, Julian D. Gillmore⁶, Guillermo A. Herrera¹⁰, Arnaud Jaccard¹¹, Dragan Jevremovic¹, Efstathios Kastritis¹², Vishal Kukreti¹³, Robert A. Kyle¹, Helen J. Lachmann⁶, Christopher P. Larsen¹⁴, Heinz Ludwig¹⁵, Glen S. Markowitz⁶, Giampaolo Merlini¹⁶, Peter Mollee¹⁷, Maria M. Picken¹⁷, Vincent S. Rajkumar¹, Virginie Royal¹ゥ, Paul W. Sanders •, Sanjeev Sethi •, Christopher P. Venner²¹, Peter M. Voorhees²², Ashutosh D. Wechalekar⁶, Brendan M. Weiss²³ and Samih H. Nasr¹

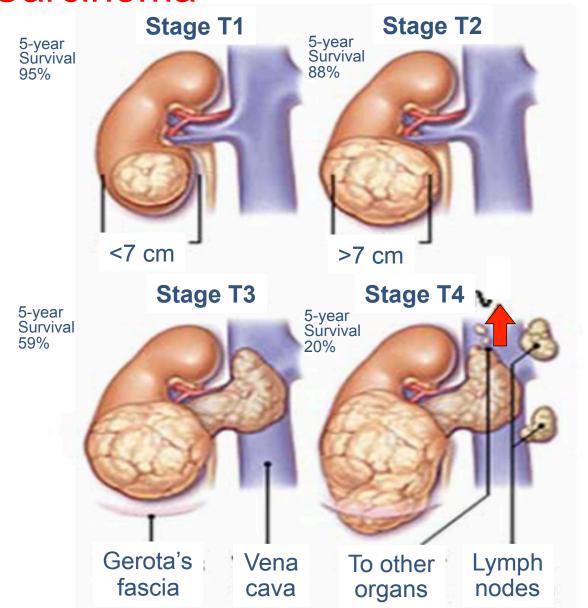


Leung N, et al. Blood 2012; Leung N, et al. Nat Rev Nephrol. 2018

Renal Cell Carcinoma

Epidemiology

- RCC accounts for ~3% of all adult malignancies
- RCC incidence is highest in
 Europe, N. America and Australia
- -Rates for new RCC have risen by
 0.7% each year over the past 10
 years (driven in part by imaging of small masses)



Onco-Nephrology Renal Cell Carcinoma Therapy

Old and New drugs

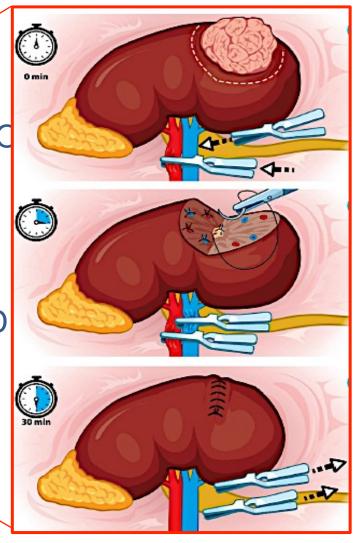
- Conventional chemotherapy
- Molecular targeted agents (anti-VEGF Abs, TKIs, mTC
- Immunotherapies (IL-2, ICP inhibitors)
- Adjuvants to surgical and percutaneous techniques

Surgical techniques

- Spare nephron loss to reduce burden of AKI and CKD
- Total vs. partial nephrectomy

Percutaneous techniques

- Cryotherapy
- Radiofrequency ablation

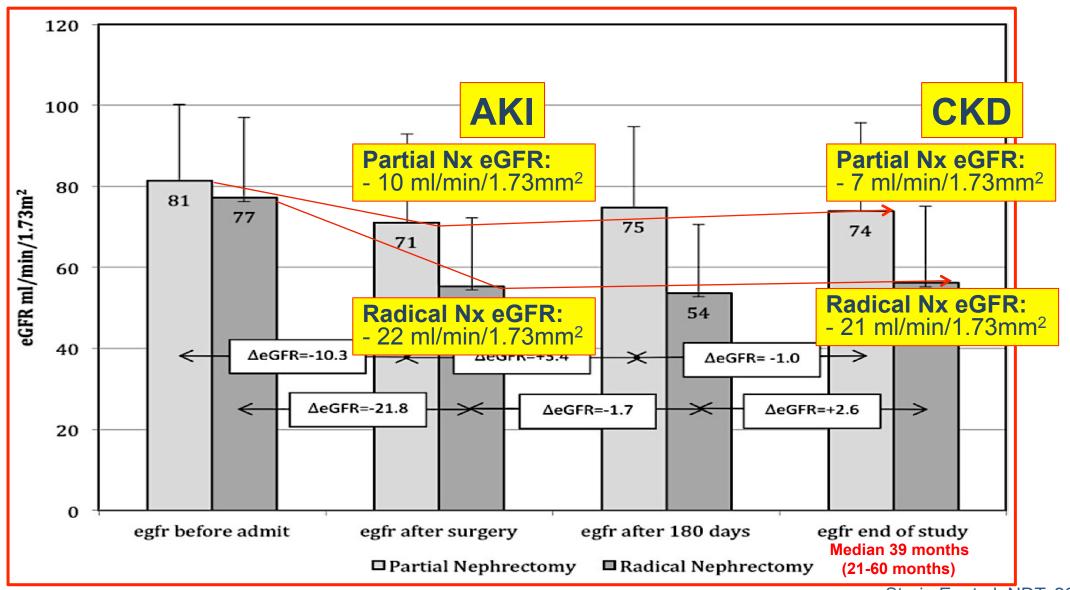


Onco-Nephrology AKI/CKD in Renal Cell Carcinoma

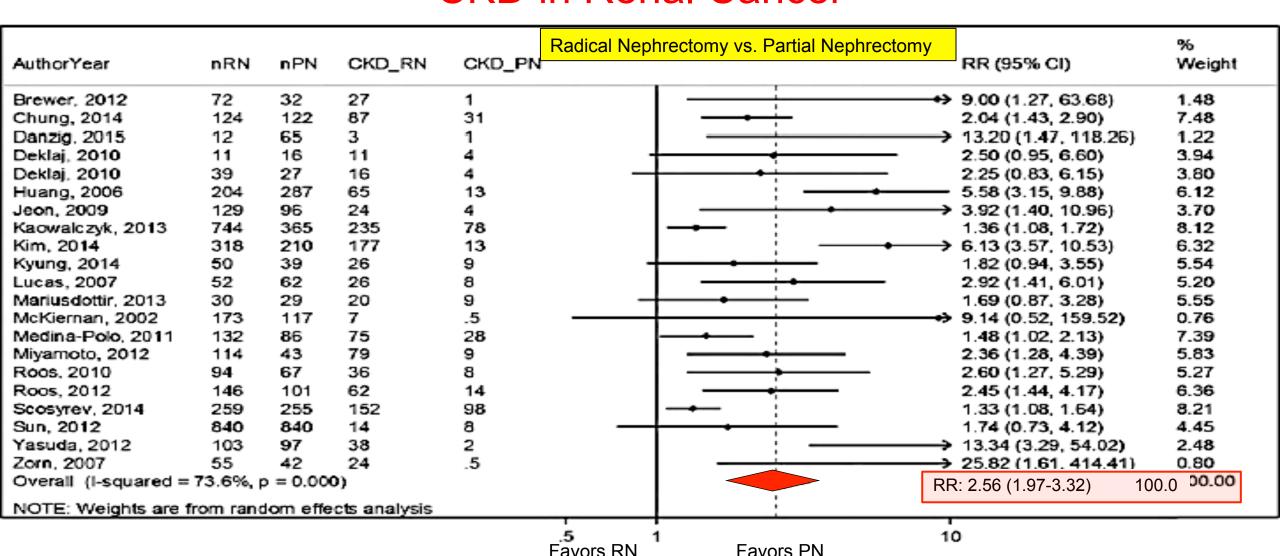
Retrospective cohort study of VA patients with RCC who underwent either PN or RN (2004-2013); N = 7073 veterans; Median 39 mo F/U

Variables	PN (Partial)	RN (Radical)
N Age (years), mean ± SD Gender (% female)	2278 62 ± 9 3.5	4795 64 ± 10 3.7
Time point eGFR	Total PN	RN
Presurgery Immediately after surgery At least 180 days postsurgery Last eGFR obtained postsurgery Median 39 months (21-60 months)	78.5 ± 19.4 81.3 60.4 ± 20.2 71.0 60.5 ± 20.5 74.8 61.9 ± 21.8 73.8	\pm 20.3 53.6 \pm 16.7

Onco-Nephrology AKI/CKD in Renal Cell Carcinoma



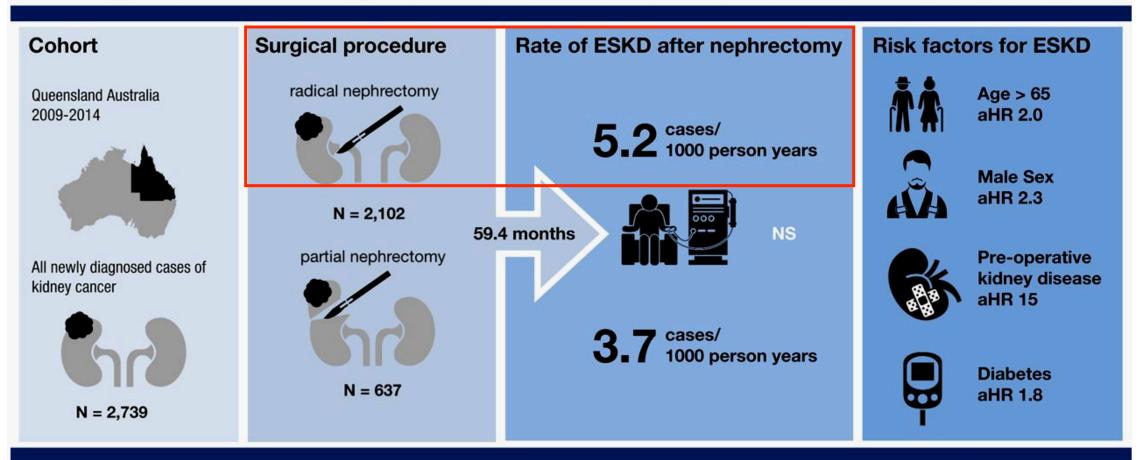
Onco-Nephrology CKD in Renal Cancer



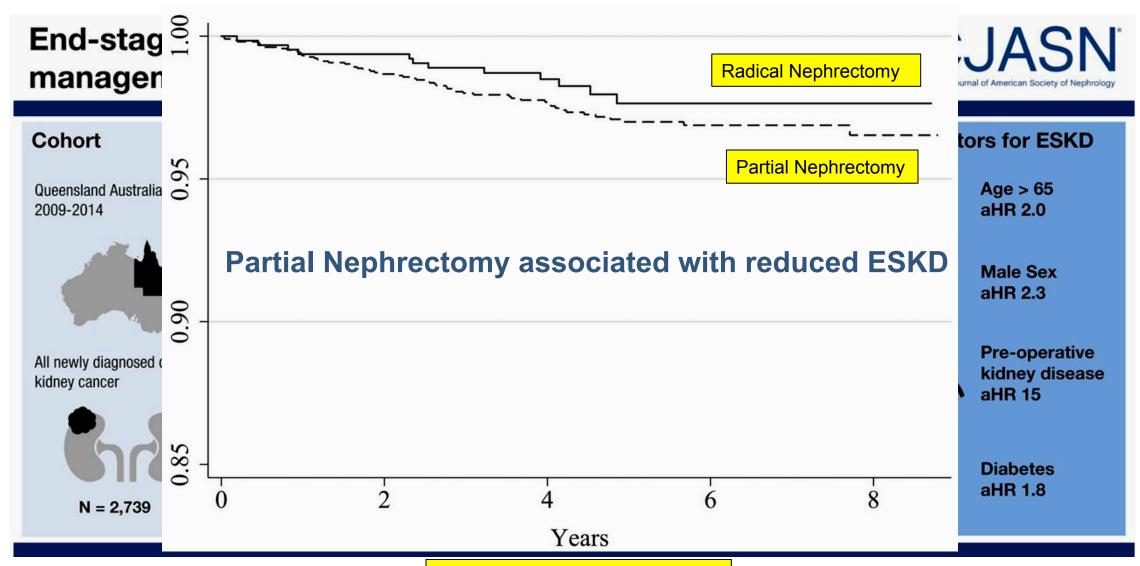
Onco-Nephrology ESKD in Renal Cancer

End-stage kidney disease following surgical management of kidney cancer

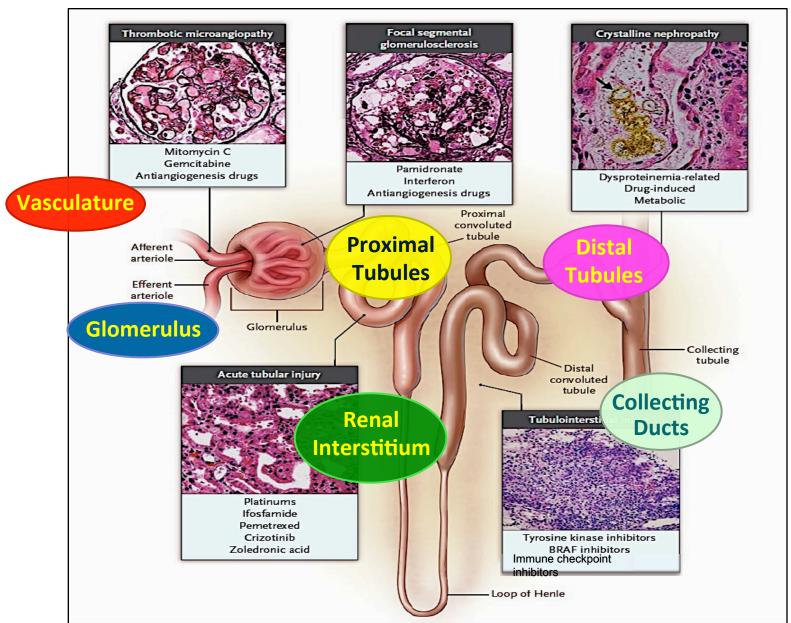




Onco-Nephrology ESKD in Renal Cancer



Anti-Cancer Drug-induced Kidney Disease



Anti-Cancer Agents

Conventional Agents

- Cytotoxic drugs (platins), Alkylating agents (ifosfamide)
- Antitumor antibiotics (mitomycin C)
- Antimetabolites (methotrexate, pemetrexed, pentostatin, gemcitabine, clofarabine)

Targeted agents

- Anti-angiogenesis drugs (anti-VEGF Ab, VEGF soluble receptors, TKIs)
- EGFR inhibitors, BRAF inhibitors, ALK inhibitors
- Proteosome inhibitors

Immunotherapies

- IL-2, interferon
- Immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PDL1)
- Chimeric antigen receptor T cells

Conventional Chemotherapeutic Agents Kidney Disease

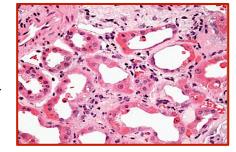
Gemcitabine, Mitcomycin C,
 Cisplatin TMA

Pamidronate

Collapsing FSGS

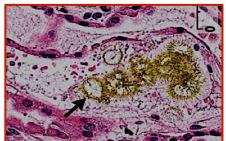


Platins, Ifosfamide, Pemetrexed,
 Zoledronate Toxic ATI/ATN



Methotrexate—

Crystalline ATI

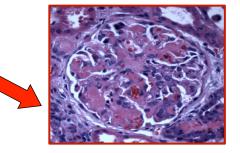


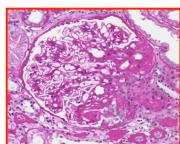
Targeted Anti-Cancer Agents

Kidney Disease

Anti-VEGF inhibitors—

TMA, MCD/FSGS

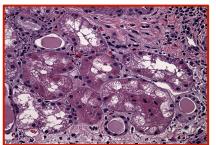




ALK inhibitors—

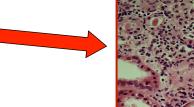
Pseudo-AKI, ATI/ATN, Renal cysts

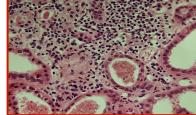




• BRAF inhibitors—

AIN/ATN

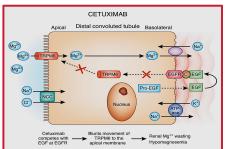




• EGFR antibodies-

Hypomagnesemia





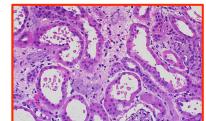
Cancer Immunotherapies

Kidney Disease

• Interleukin-2-

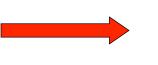
Prerenal AKI, ATN, PI-GN

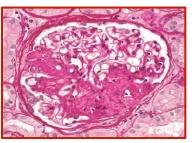


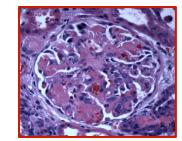


Interferon—

FSGS/TMA

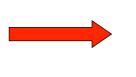


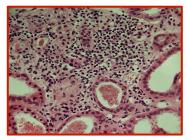


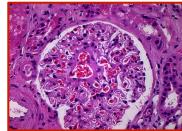


Immune Checkpoint

Inhibitors— AIN/IC-GN/MCD Txp rejection







• CAR T-Cells-

Prerenal AKI/ATI, TLS, electrolyte disorders







Cancer Immunotherapies

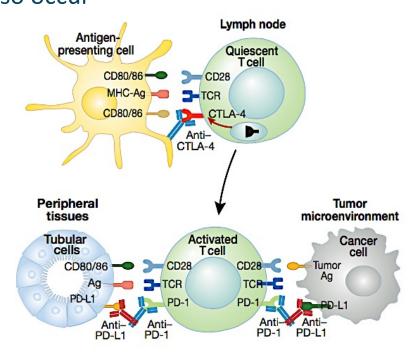
Immune Checkpoint Inhibitors and Kidney Disease

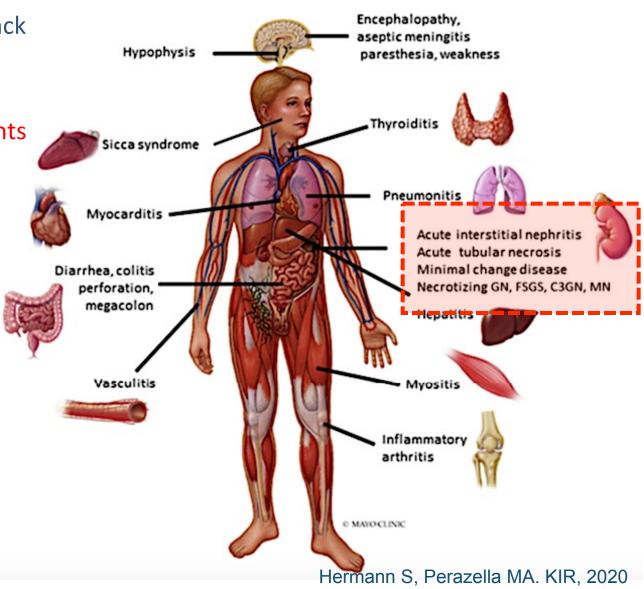
 ICPIs blunt immune checkpoints to allow T-cells to attack various cancers

Monoclonal Abs against CTLA-4, PD-1 and PD-L1

ICPIs are complicated by immune-related adverse events

 AKI incidence of 2-5% due primarily to ATIN, but other lesions also occur





Cancer Immunotherapies CAR T-Cell and Kidney Disease

Cytokine Release Syndrome

Perazella MA, Shirali AC. JASN 2018

Tocilizumab reduces CRS by blocking

IL-6 from binding to its receptor

Hemophagocytic

IL-6 Receptor

Infusion of CAR T-Cells

release Cytokines

CAR T-Cell

CAR T-Cell

Cancer Cell

CAR T-Cells Engage Cancer Cells

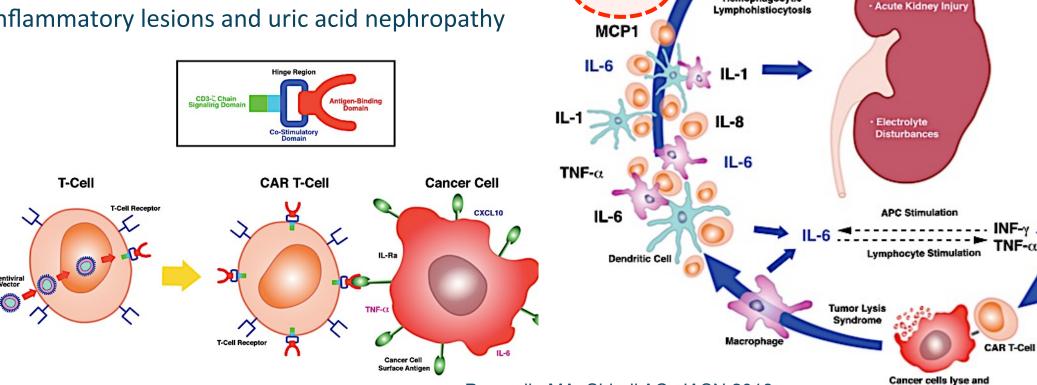
CAR T-Cells Proliferate

 Harvest host T cells to create CAR T-cells to target cancers

• CD19, CD20, and CD30, etc. are the cancer Ag targets

CAR T-cell therapy is complicated by CRS, HLH and TLS

 AKI is primarily prerenal and ATI, but may also have inflammatory lesions and uric acid nephropathy



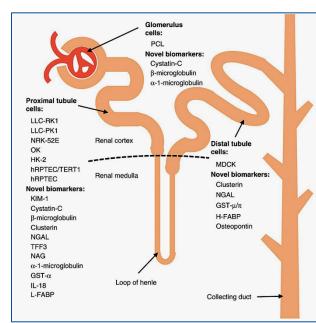
Onco-Nephrology What do we need to do?

- Basic Research in Onco-Nephrology
- Clinical Research in Onco-Nephrology
- Clinical Care in Onco-Nephrology

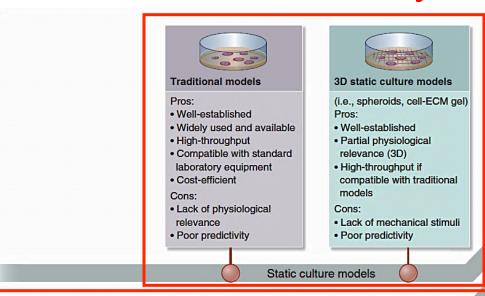
Onco-Nephrology What do we need to do?

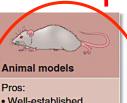
Basic Research in Onco-Nephrology

- Preclinical studies of anti-cancer agents to evaluate
 - safety and nephrotoxicity
 - Employ novel kidney injury biomarkers
 - FDA and EMA approved 7 biomarkers
- Utilize kidney on a chip technology



Kidney on a Chip Technology





- Well-established
- Physiological relevance
- Complete organism
- Species differences
- Poor predictivity
- Ethical concerns High costs

Cons:



Static Culture/Animal Models

- Cell cultures-well established, no or partial physiological relevance; high throughput and cost efficient
- Animal models-have physiological relevance, but costly with ethical concerns and species differences
- Both Poorly Predictive of Nephrotoxicity

Next-generation models

- Enhanced in vivo like complexity and functionality (e.g., vascularization and renal functionality)
- Fully validated
- User-friendly
- Cost-efficient
- Highly predictive
- Hyphenation for real-time "omics" profiling
- Replacement of animal

Microfluiditic Culture Models

- Have Physiological Relevance
- Laborious, Lack of Validation

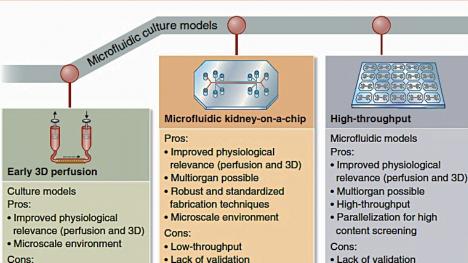
- Have Physiological Relevance
- User friendly
- Cost efficient
- Highly predictive of nephrotoxicity
- Replace animal models

- Highly specialized

 Very laborious Low-throughput

Lack of validation

 Not compatible with standard screening tools Lack of validation



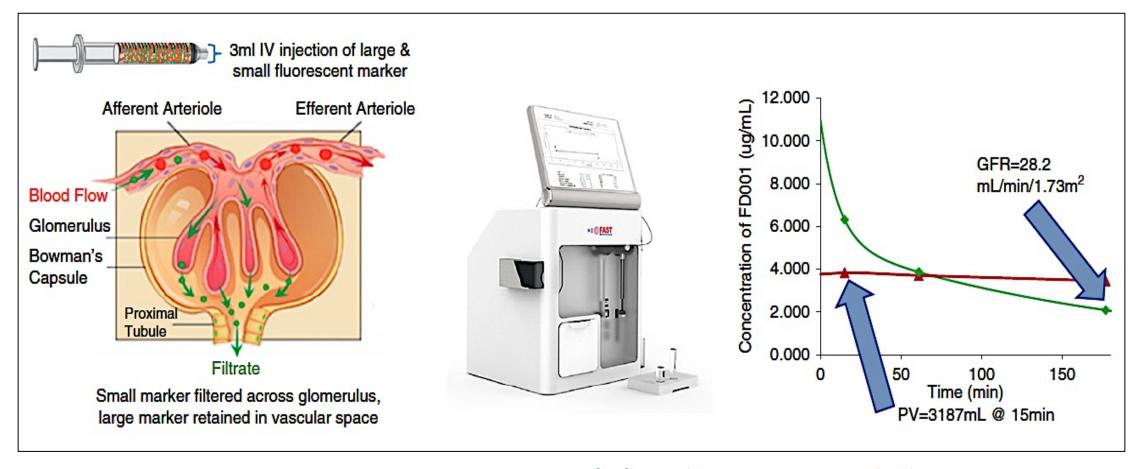
Ashammakhi N, et al. KI 2018

Onco-Nephrology What do we need to do?

Clinical Research in Onco-Nephrology

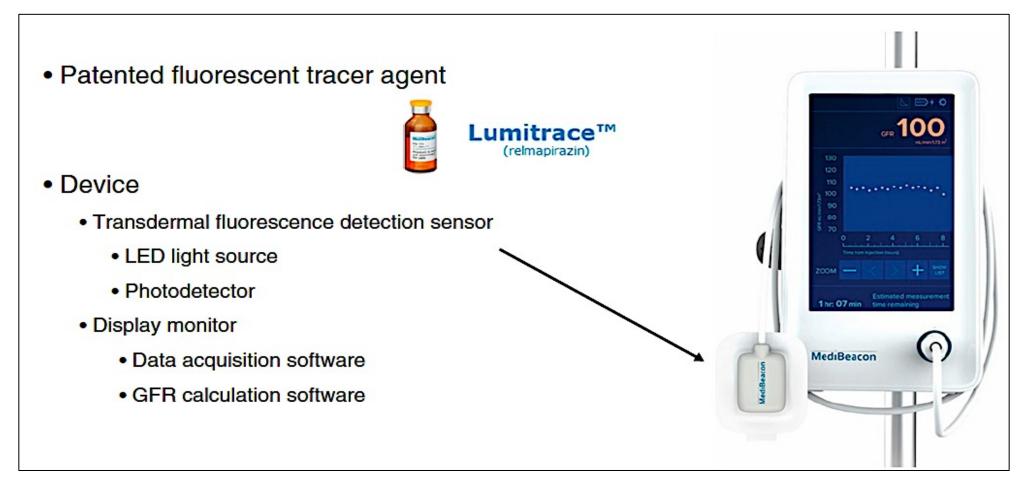
- Develop better GFR estimates for <u>drug dosing</u> in <u>cancer/</u>
 <u>CKD patients</u>
- Include CKD patients in Clinical Oncology Trials
- Utilize Novel Biomarkers in Clinical Oncology Trials?
- Develop POC tests that rapidly provide 'measured GFR' in cancer patients

POC tests that provide 'measured GFR'



FAST BioMedical technique to measure both GFR and plasma volume (PV). Two fluorescent markers of different molecular mass are injected: 1) small freely filtered 5-kD FITC-labeled carboxymethyl dextran and 2) large 150-kD rhodamine-labeled carboxymethyl dextran that is not filtered across the glomerulus. At three time points, a blood sample is drawn, and fluorescence is detected using a fluorometer. The raw data are converted using a software package to PV from the 15-minute sample and to measured GFR from all three samples.

POC tests that provide 'measured GFR'



MediBeacon transdermal GFR measurement system. The patient is administered a fluorescent tracer agent that is removed from the blood exclusively by GFR, and measured fluorescence decreases over time as the substance is cleared by the kidney through GFR. A display monitor used algorithms to calculate GFR.

Onco-Nephrology What do we need to do?

Clinical Care in Onco-Nephrology

- Establish collaborative Onco-Nephrology Clinics
- Enhance education in Onco-Nephrology
- Promote collaboration in Onco-Nephrology

Nephrol Dial Transplant (2018) 33: 1503–1510 doi: 10.1093/ndt/gfy188 Advance Access publication 5 July 2018

Onco-Nephrology Clinic



Opening an onconephrology clinic: recommendations and basic requirements

Laura Cosmai^{1,*}, Camillo Porta^{2,*}, Mark A. Perazella³, Vincent Launay-Vacher⁴, Mitchell H. Rosner⁵, Kenar D. Jhaveri⁶, Matteo Floris⁷, Antonello Pani⁷, Cécile Teuma⁸, Cèzary A. Szczylik⁹ and Maurizio Gallieni^{1,10}

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Onco-Nephrology ASN Educational Curriculum-2016

Online Curricula: Onco-Nephrology



Introduction to the American Society of Nephrology Onco-Nephrology Curriculum

This series of 19 chapters covers most of the important Onco-Nephrology topics. The chapters include Take Home Points and Board style questions to highlight important issues. The goal is to provide ASN members, including veteran nephrologists, newly minted nephro-clinicians, and fellowship trainees, as well as other interested healthcare providers, the building blocks upon which further information can be added as the field advances. I hope the curriculum provides the initial framework to achieve this goal.

For more information about the curriculum, the Society's efforts related to Onco-Nephrology, or ASN, please contact policy@asn-online.org or 202-640-4660.

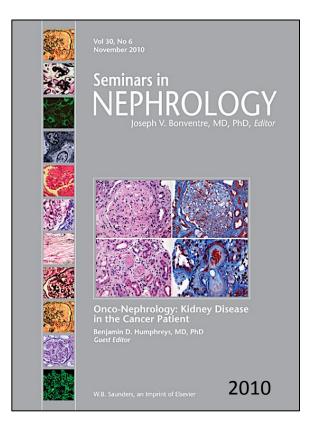
Mark A. Perazella, MD American Society of Nephrology

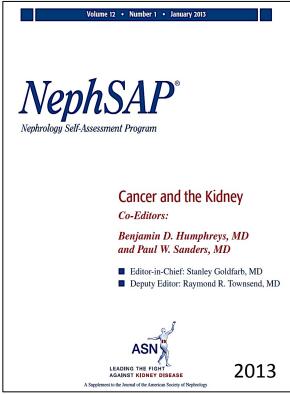
Onco-Nephrology ASN Educational Curriculum-2016

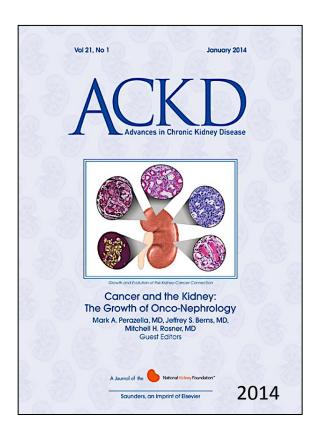
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Onco-Nephrology Educational Textbooks and Journals









Educational Symposia and Conferences

Internatio

Onco

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In Medicin

Prof. Giovambattista Capasso

• Cuiversià degli Studi riella Campania Ingel Law delli

Prof. Fortunato Ciardiello

Organized by



Onco-Nephrolog Cancer and the

Course Description

treatment. This program provides associated with cancer. The progra with cancer, emphasizing evidence newer targeted biological anti-neo kidneys, and its treatment are pres transplants are reviewed. This pro of the patient following nephrecton malignancies in patients with CKD

ASN designates this live activity for

Course Objective(s)

Upon completion of this program, function; 2) know how to treat acut the effects of antineoplastic therap with ESRD.

Co-Chairs

- · Jeffrev S. Berns, MD, FASN
- Mitchell H. Rosner, MD. FASN

Sessions

November 9, 2011 | 07:00 AM - 06 Location: 202 | 77



NORTH SHORE-LIJ HEALTH SYSTEM FACU Thomas P. Bradley, MD* Steven Fishbane, MD* Kenar D. Jhaveri, MD* Hitesh H. Shah, MD

VISITING FACULTY Gerald B. Appel, MD Joseph Bonventre, MD, Pl Bradley P. Dixon, MD Glenn S. Markowitz, MD Naveed Masani, MD Vinay Nair, DO Mark A. Perazella, MD



*Course Directors





MD Andersor Onco-Nei

Friday, October 14, 2010



ONC NEPH

DECEMBER '

Memorial Sloan Kett Zuckerman Researc 417 East 68th Street New York, NY 10065



THE UNIVERSITY O MD Ande Making Cancer History



MDAnderson Cancer Center KDIGO executive conclusions

www.kidney-international.org

KDIGO Controversies Conference on onco-nephrology: understanding kidney impairment and solid-organ malignancies, and managing kidney cancer



Camillo Porta¹, Aristotelis Bamias², Farhad R. Danesh³, Alicja Debska-Ślizień⁴, Maurizio Gallieni⁵, Morie A. Gertz⁶, Jan T. Kielstein⁷, Petra Tesarova⁶, Germaine Wong^{9,10}, Michael Cheung¹¹, David C. Wheeler ^{12,13}, Wolfgang C. Winkelmayer¹⁴ and Jolanta Malyszko¹⁵; for Conference Participants ¹⁶

Department of Internal Medicine and Therapeutics, University of Pavia and Division of Translational Oncology, IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy, "Second Propaedeutic Department of Internal Medicine, National and Kapadistrian University of Athens. Greece: Section of Nephrology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; Clinical Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdańsk, Gdańsk, Poland; ^sNephrology and Dialysis Unit, Luigi Sacco Department of Biomedical and Clinical Sciences, Università di Milano, Milan, Italy; Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Minnesata, USA: *Medical Clinic V, Nephrology, Rheumatology, Blood Purification, Academic Teaching Hospital Braunschweig, Braunschweig, Germany; *Department of Oncology, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; *Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, New South Wales, Australia; 16 Sydney School of Public Health, University of Sydney, New South Wales, Australia; 11 KDIGO, Brussels, Belgium; ¹²Department of Renal Medicine, University College Landon, Landon, UK; ¹³George Institute for Global Health, Sydney, Australia; ¹⁴Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA: and 15 Department of Nephrology, Dialysis, and Internal Medicine, Medical University of Warsaw, Poland

The association between kidney disease and cancer is multifaceted and complex. Persons with chronic kidney disease (CKD) have an increased incidence of cancer, and both cancer and cancer treatments can cause impaired kidney function. Renal issues in the setting of malignancy can worsen patient outcomes and diminish the adequacy of anticancer treatments. In addition, the oncology treatment landscape is changing rapidly, and data on tolerability of novel therapies in patients with CKD are often lacking. Caring for oncology patients has become more specialized and interdisciplinary, currently requiring collaboration among specialists in nephrology, medical oncology, critical care, clinical pharmacology/pharmacy, and palliative care, in addition to surgeons and urologists. To identify key management issues in nephrology relevant to patients with malignancy, KDIGO (Kidney Disease: Improving Global Outcomes) assembled a global panel of multidisciplinary clinical and scientific expertise for a controversies conference on onconephrology in December 2018. This report covers issues related to kidney impairment and solid organ

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malignancies as well as management and treatment of kidney cancer. Knowledge gaps, areas of controversy, and research priorities are described.

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KEYWORDS: glomerular filtration rate: nephrotoxicity; oncology; renal cell

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idney disease and cancer have a multifaceted association. Persons with chronic kidney disease (CKD) have an increased incidence of cancer relative to patients without CKD. 1.2 In addition, both cancer and cancer treatments can cause impaired kidney function, including acute kidney injury (AKI) or CKD. Renal issues in the setting of malignancy can worsen patient outcomes and diminish the adequacy of anticancer treatments. Patients whose cancer is potentially curable can experience multiorgan failure requiring intensive care and kidney replacement therapy. In some countries, the amelioration of cancer mortality caused by greater treatment efficacy has resulted in a growing population of cancer survivors' who are at increased risk for kidney disease. Finally, advanced malignancy complicated by multiorgan illness raises questions related to the appropriateness of aggressive treatment versus palliative therapy.

The complex relationship between kidney disease and cancer is confounded by a rapidly changing treatment landscape. Caring for oncology patients has become more

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Onco-Nephrology Collaboration

- National (AIOM, SIN) and International Scientific Society Conferences (EDTA, ASN) with onco-nephrology sessions and educational courses
- National Oncological and Urological conferences
- Epidemiological studies in Italy (surveys and other projects in progress)
- Papers published in International Journals; Textbooks on Onco-Nephrology
- Urological Guidelines on kidney cancer (AURO 2012)
- AIOM Guidelines on kidney cancer (2015-2016-2017-2018)
- TMD Project (Italian Multidisciplinary Group on GU cancers)
- Collaboration between Nefrological e Oncological International Society
- Interdisciplinary Working Group on Onco-Nephrology (AIOM-SIN) dedicated to specific projects (i.e., contrast medium use in cancer patients)



















Thank You!