

Berliner Dialyse Seminar

Onco-Nephrology: An Emerging New Discipline

Mark A. Perazella, MD
Professor of Medicine
Section of Nephrology
Yale University School of Medicine
and West Haven VA Medical Center



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 **no conflicts of interest** 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

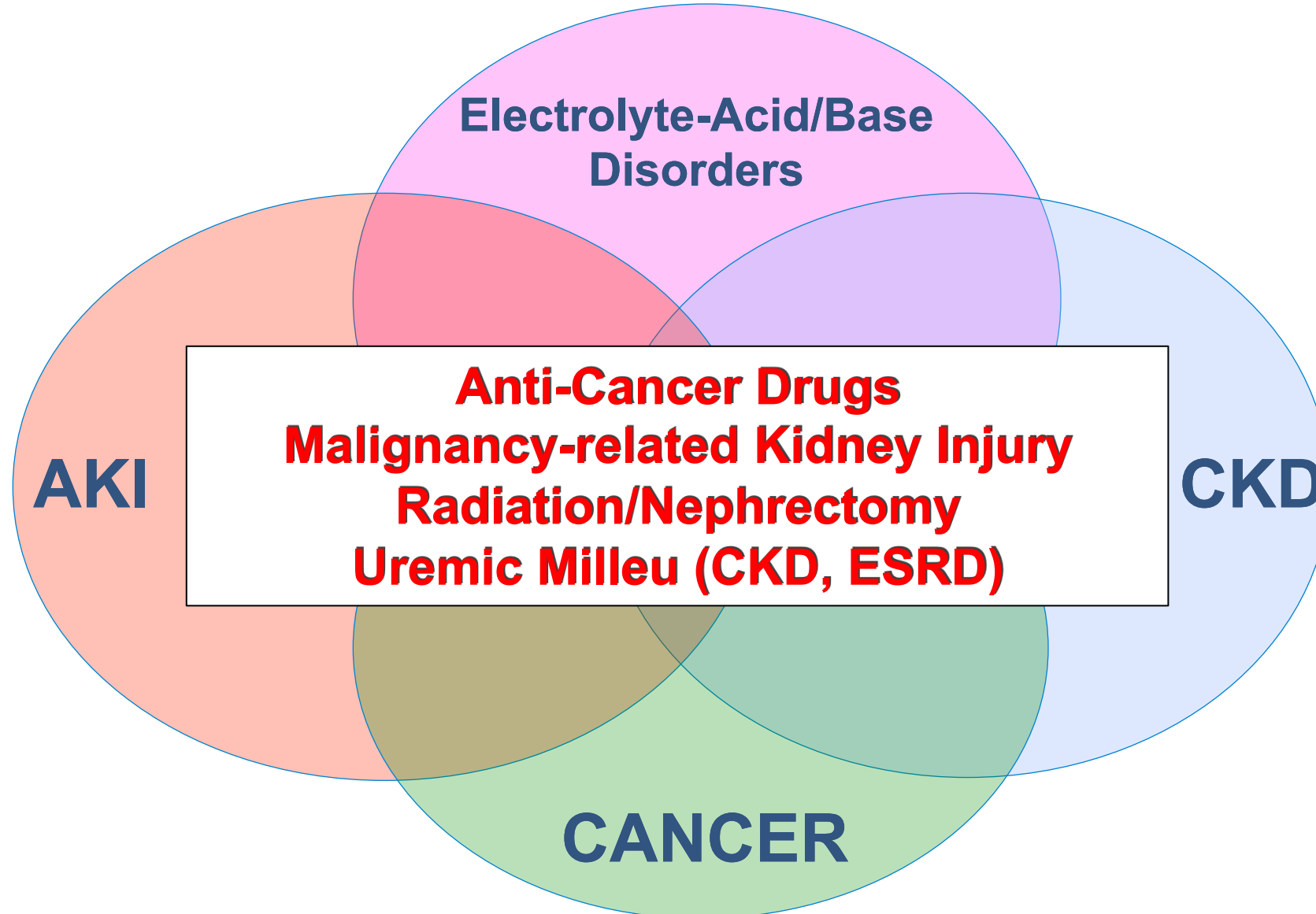
A Common Global Problem

- 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



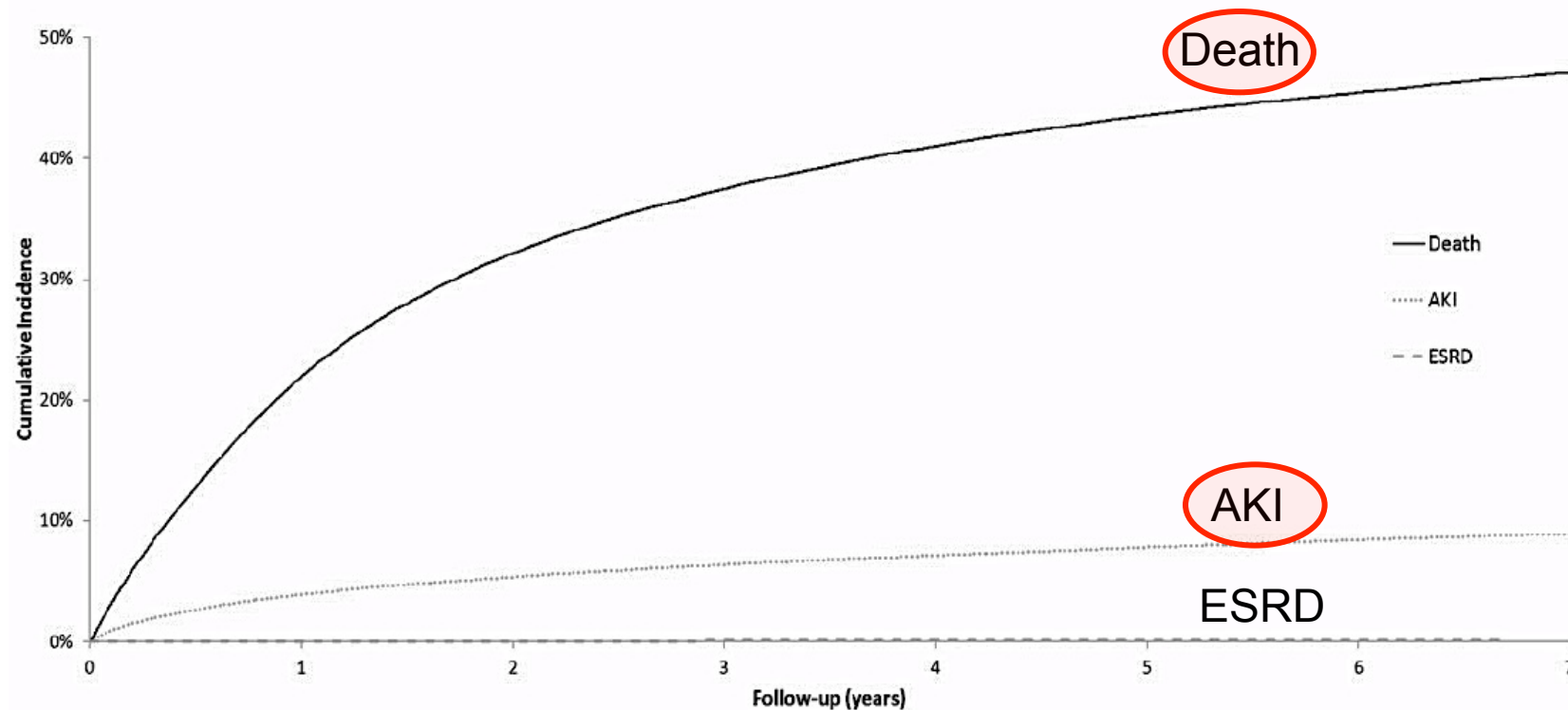
Onco-Nephrology

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%)

2007-2014

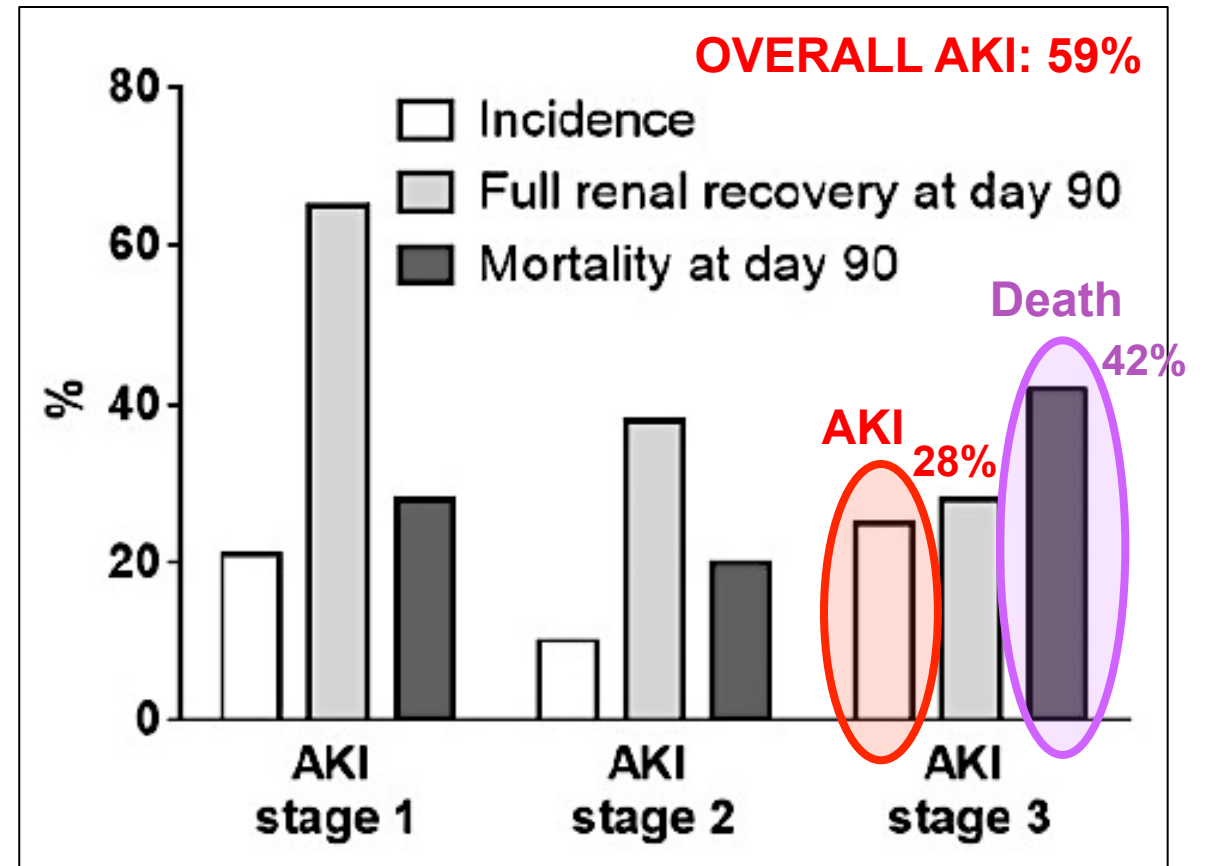


Onco-Nephrology

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

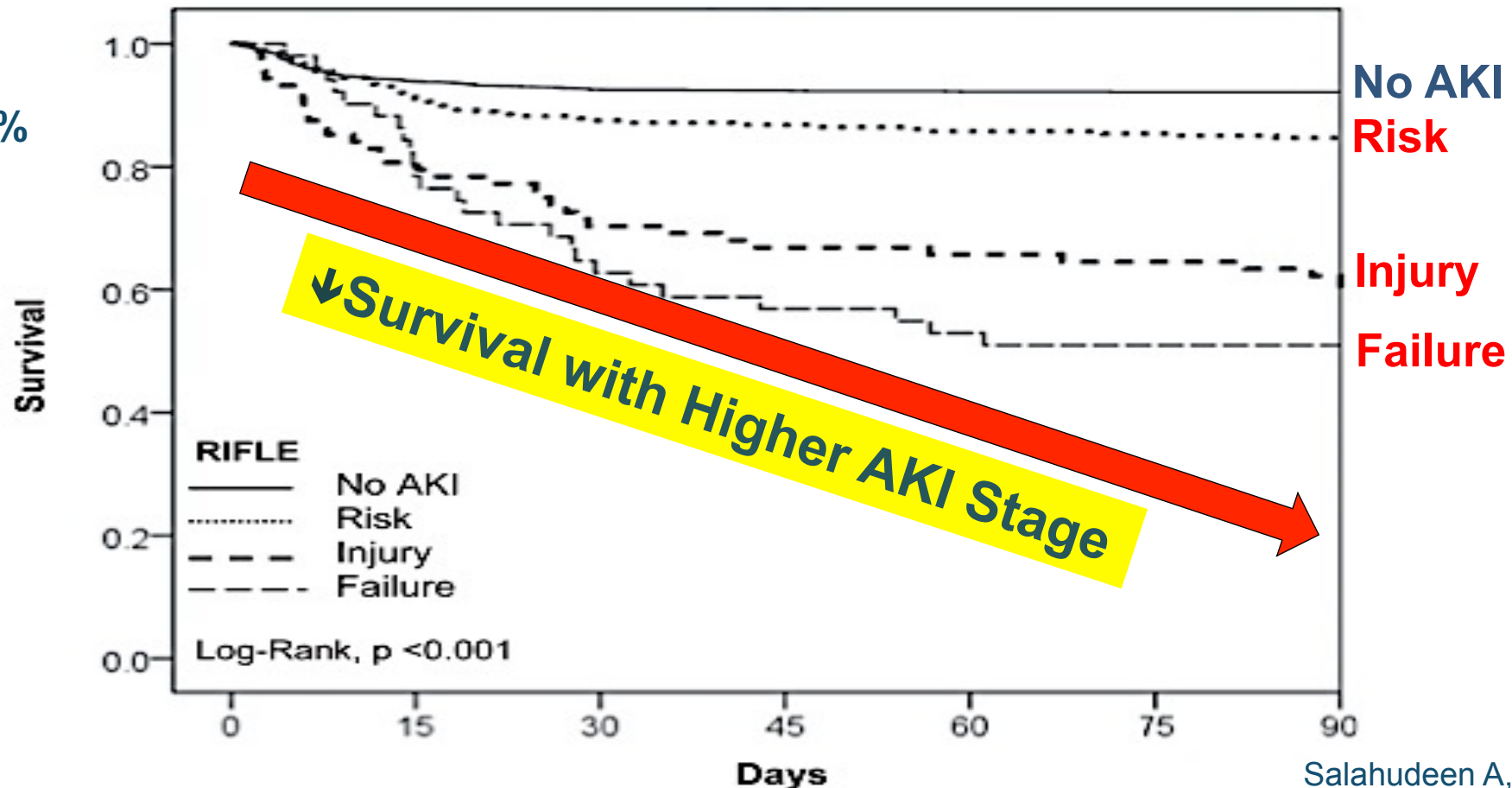


Onco-Nephrology

Increased Mortality with AKI

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

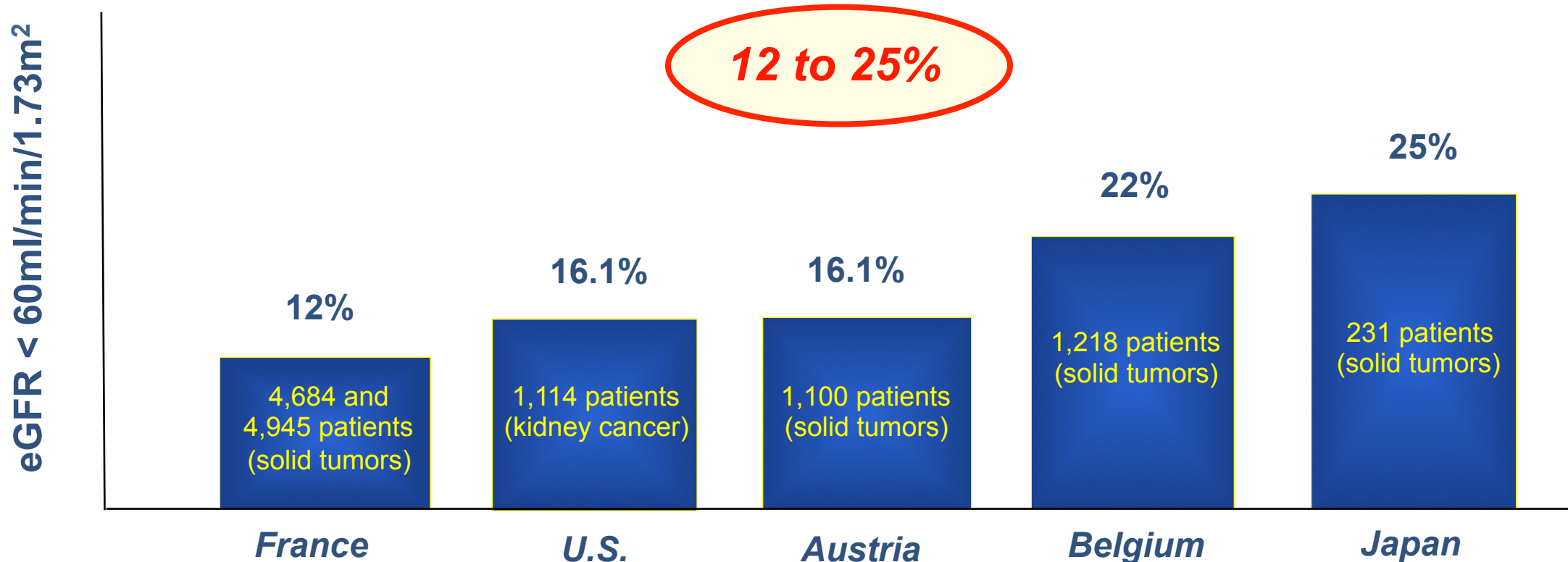
Overall AKI
Incidence = 12%



Onco-Nephrology

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

Proximal Tubular

- Light Chains
- Drugs

Interstitial

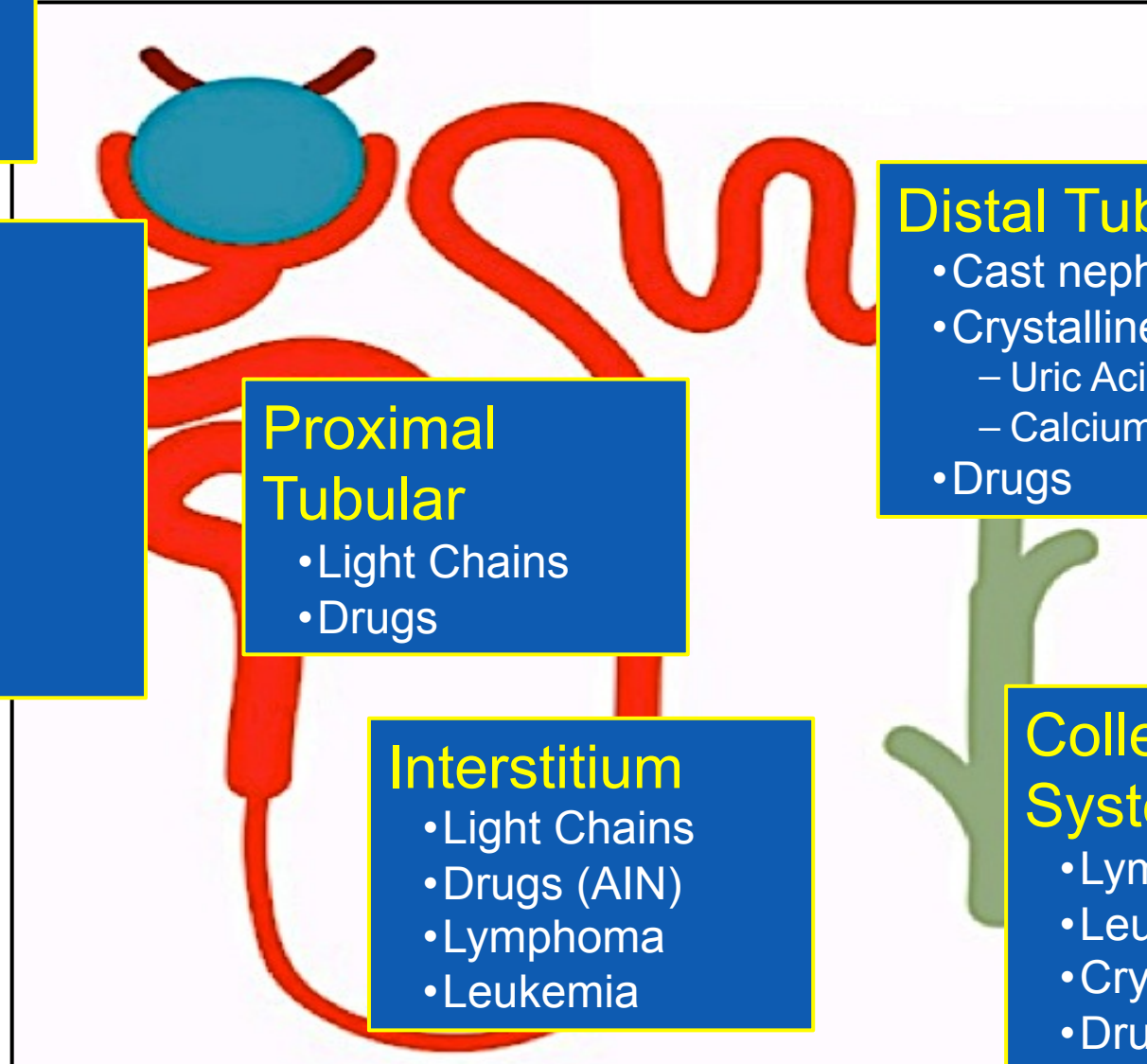
- Light Chains
- Drugs (AIN)
- Lymphoma
- Leukemia

Distal Tubular

- Cast nephropathy
- Crystalline nephropathy
 - Uric Acid
 - Calcium Phosphate
- Drugs

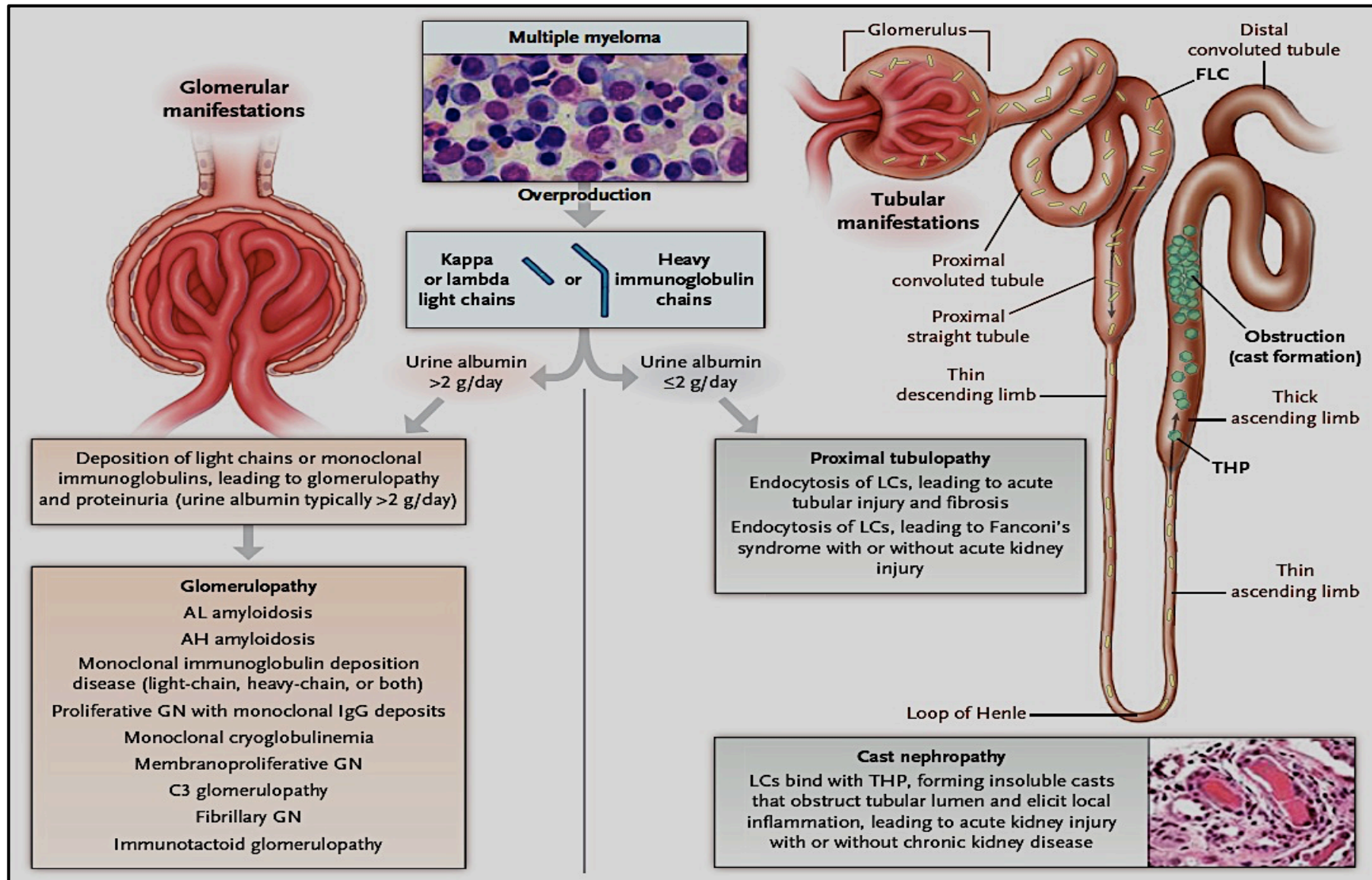
Collecting System

- 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)	

Onco-Nephrology

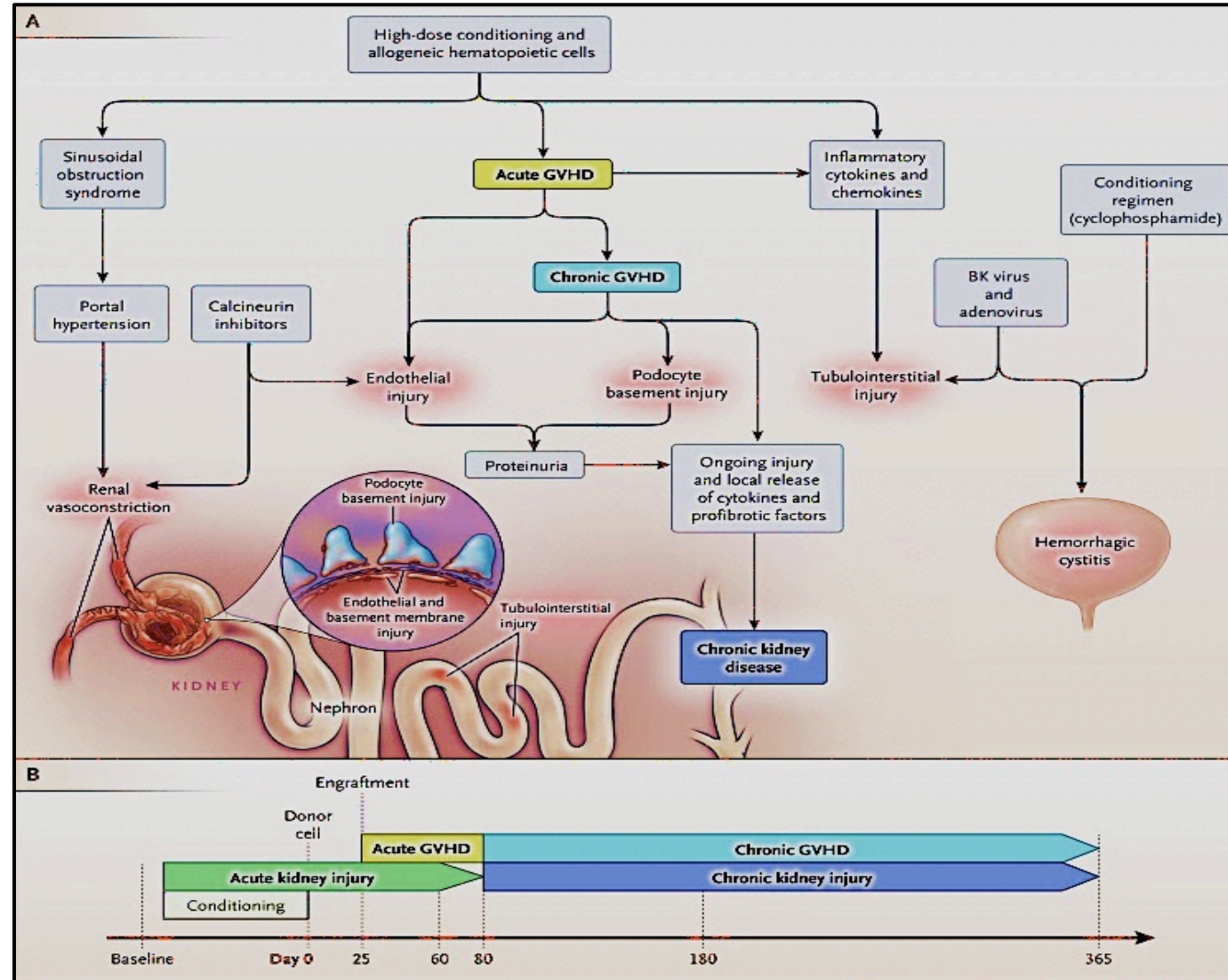
Hematopoietic Stem Cell Transplant and Kidney Disease

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			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 histiocytosis	Fibrillary GN*	GOMMID	HCDD	Macroglobulinemia

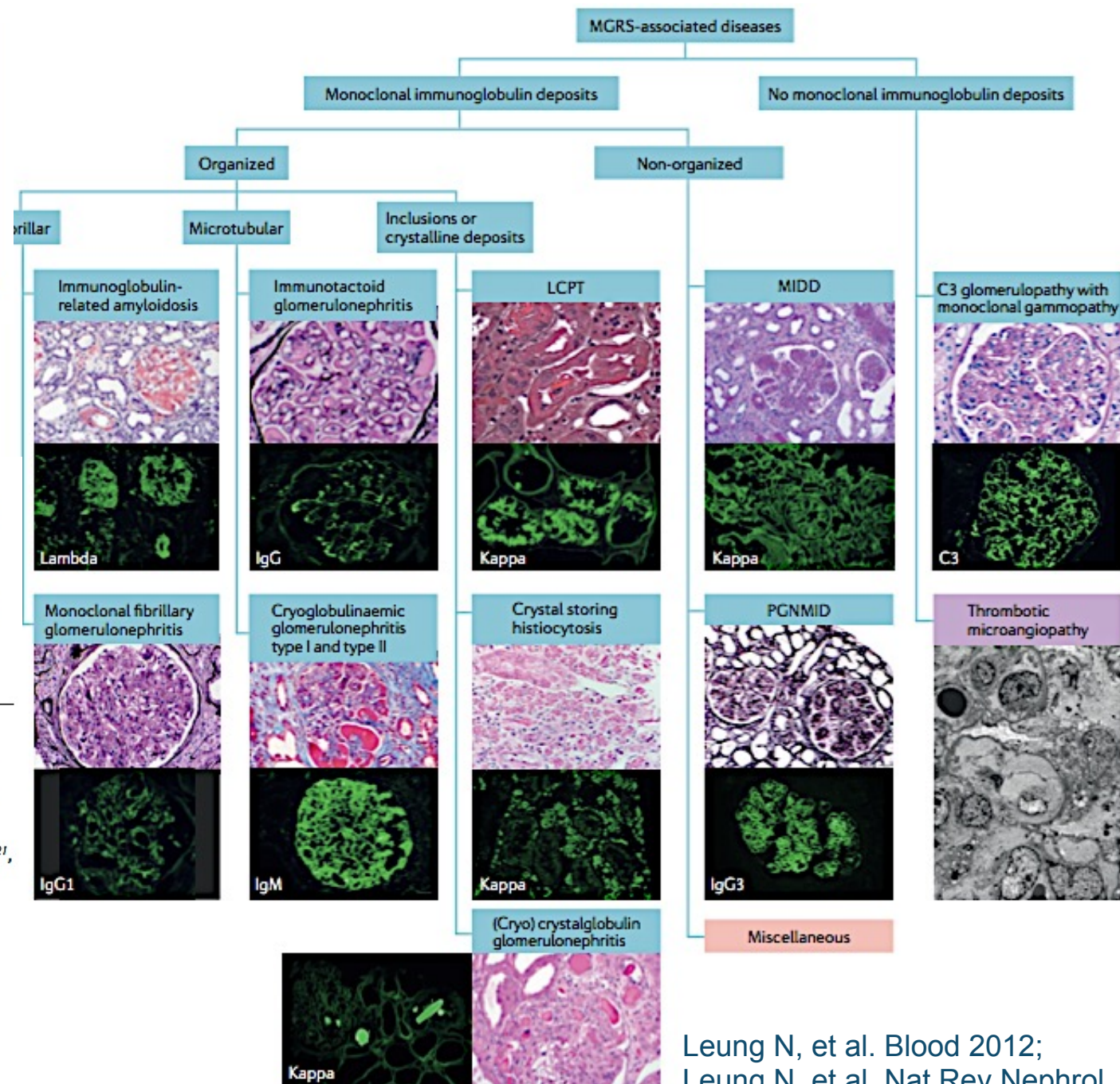
- Therapy initiated to reduce paraproteins
 - Prevent acute kidney injury (or help reverse AKI) and prevent development of future CKD

CONSENSUS STATEMENT

EXPERT CONSENSUS DOCUMENT

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

Nelson Leung¹*, Frank Bridoux², Vecihi Batuman³, Aristeidis Chaidos⁴, Paul Cockwell⁵, Vivette D. D'Agati⁶, Angela Dispenzieri¹, Fernando C. Fervenza¹, Jean-Paul Fermand⁷, Simon Gibbs⁸, Julian D. Gillmore⁹, Guillermo A. Herrera¹⁰, Arnaud Jaccard¹¹, Dragan Jevremovic¹, Efsthios Kastiris¹², Vishal Kukreti¹³, Robert A. Kyle¹, Helen J. Lachmann⁹, Christopher P. Larsen¹⁴, Heinz Ludwig¹⁵, Glen S. Markowitz⁶, Giampaolo Merlini¹⁶, Peter Mollee¹⁷, Maria M. Picken¹⁸, Vincent S. Rajkumar¹, Virginie Royal¹⁹, Paul W. Sanders²⁰, Sanjeev Sethi¹, Christopher P. Venner²¹, Peter M. Voorhees²², Ashutosh D. Wechalekar⁹, Brendan M. Weiss²³ and Samih H. Nasr¹

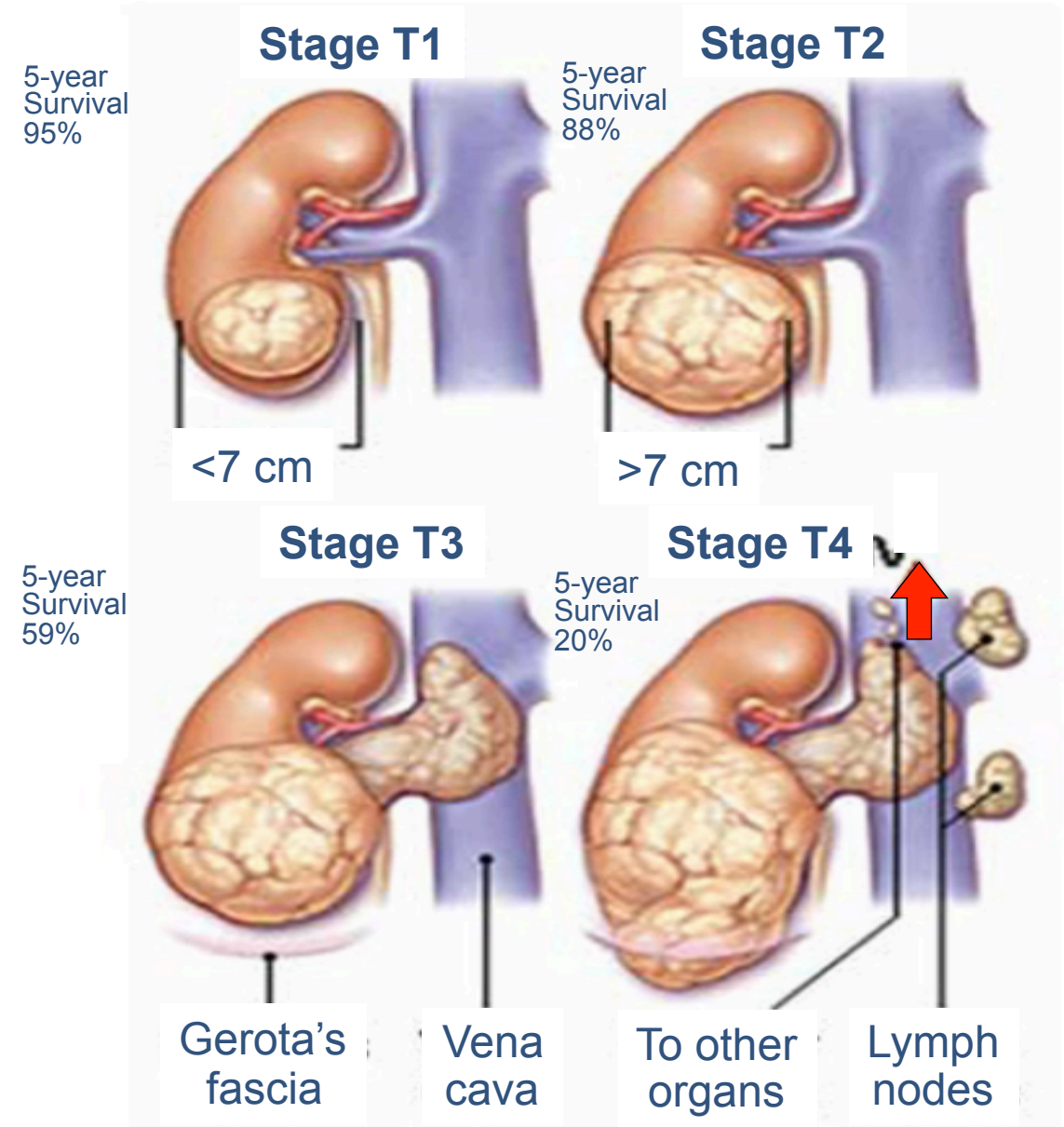


Onco-Nephrology

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**

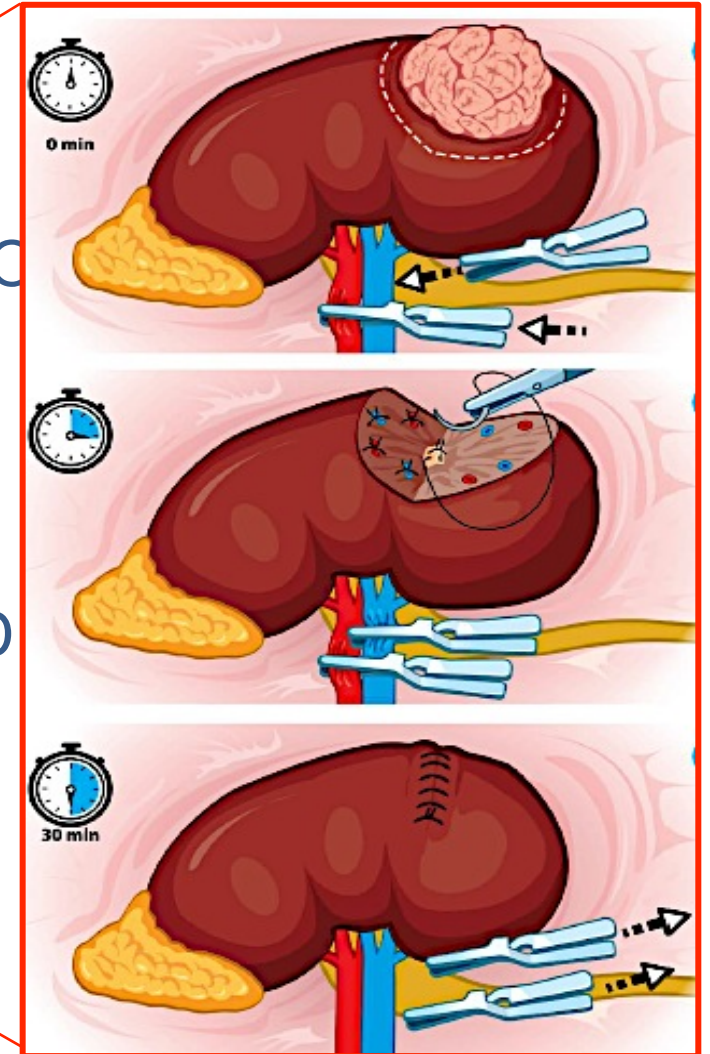
- Conventional chemotherapy
- Molecular targeted agents (anti-VEGF Abs, TKIs, mTOR inhibitors)
- Immunotherapies (IL-2, ICP inhibitors)
- Adjuvants to surgical and percutaneous techniques

- **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

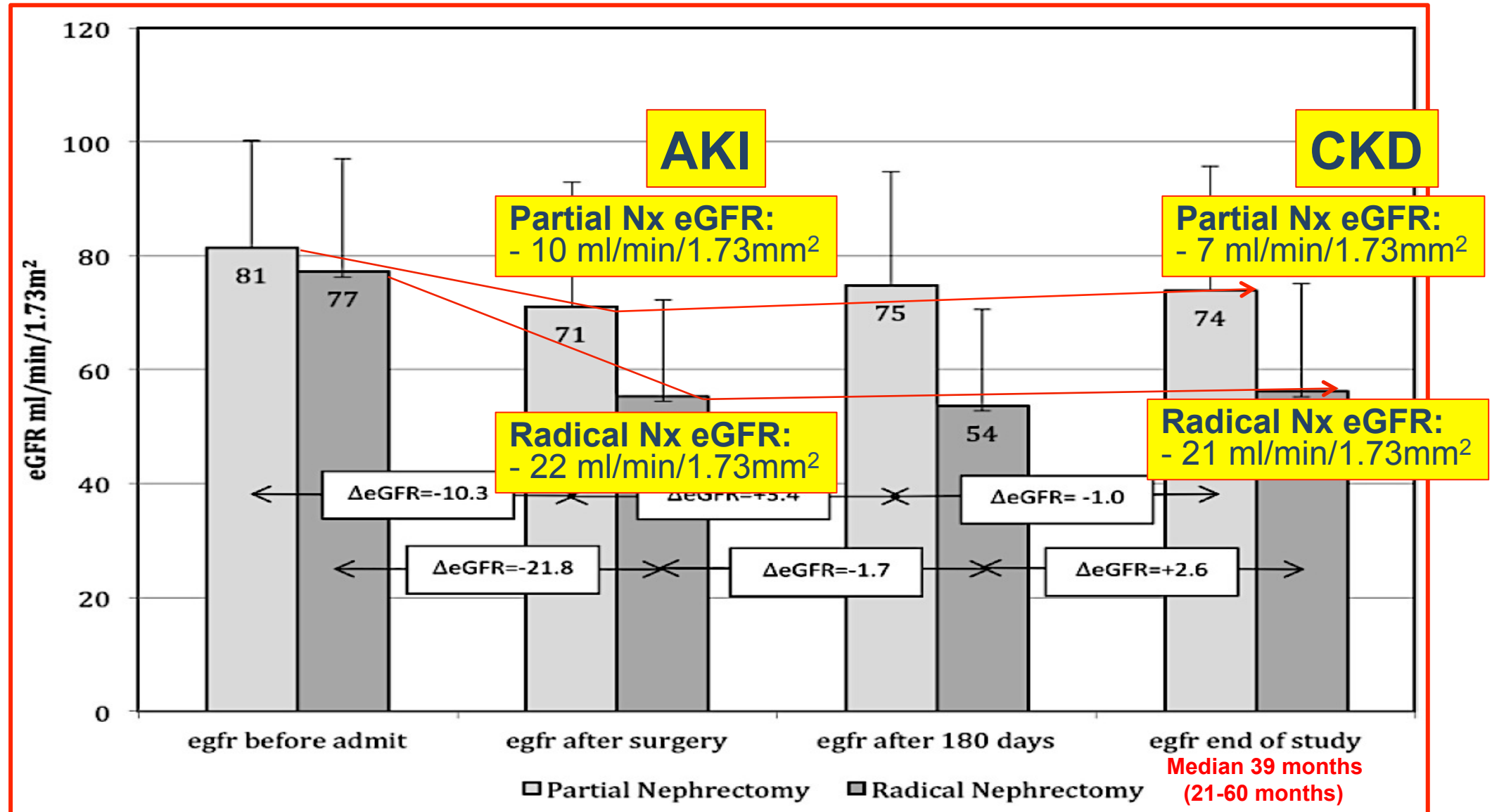
- Retrospective cohort study of VA patients with RCC who underwent either PN or RN (2004-2013); N = 7073 veterans; Median 39 mo F/U

Variables		PN (Partial)	RN (Radical)
N		2278	4795
Age (years), mean ± SD		62 ± 9	64 ± 10
Gender (% female)		3.5	3.7

Time point	eGFR	Total	PN	RN
Presurgery		78.5 ± 19.4	81.3 ± 18.9	77.2 ± 19.6
Immediately after surgery		60.4 ± 20.2	71.0 ± 22.2	55.3 ± 17.0
At least 180 days postsurgery		60.5 ± 20.5	74.8 ± 20.3	53.6 ± 16.7
Last eGFR obtained postsurgery	Median 39 months (21-60 months)	61.9 ± 21.8	73.8 ± 21.9	56.2 ± 19.3

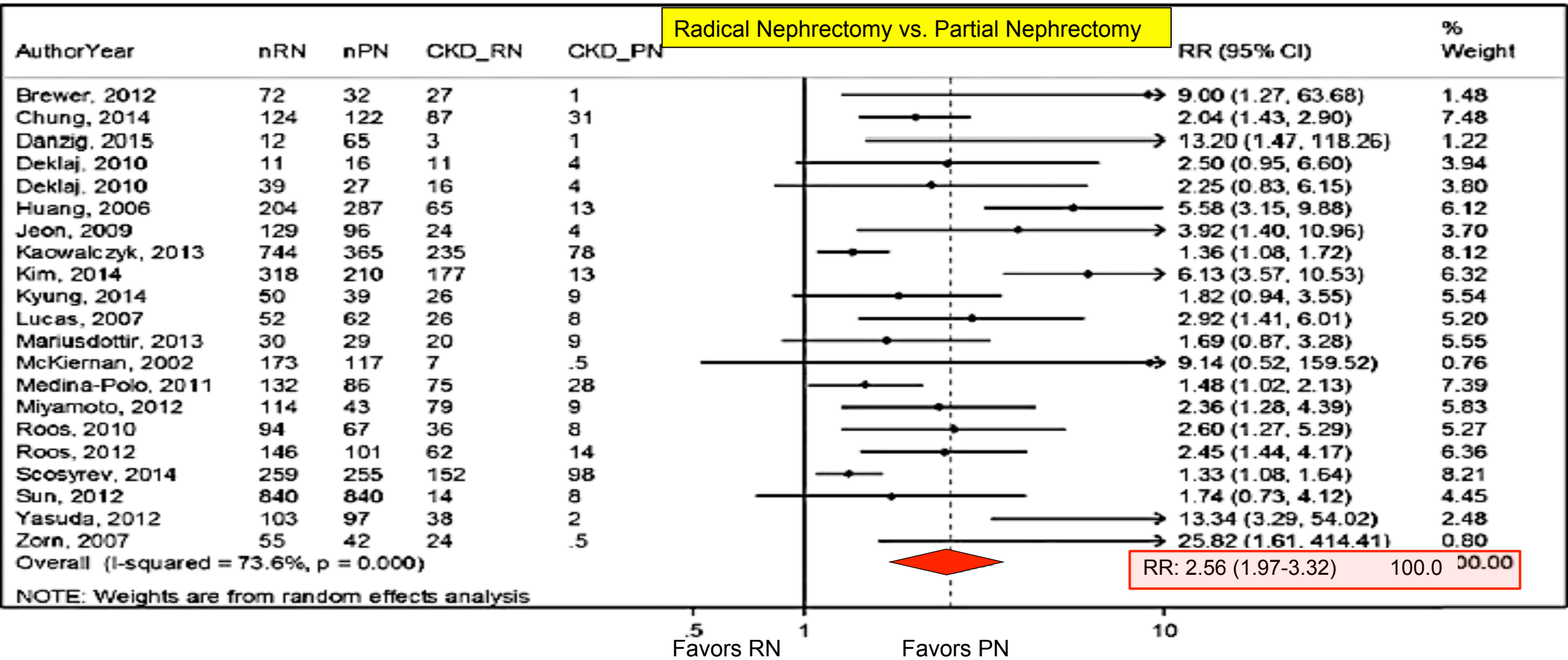
Onco-Nephrology

AKI/CKD in Renal Cell Carcinoma



Onco-Nephrology

CKD in Renal Cancer



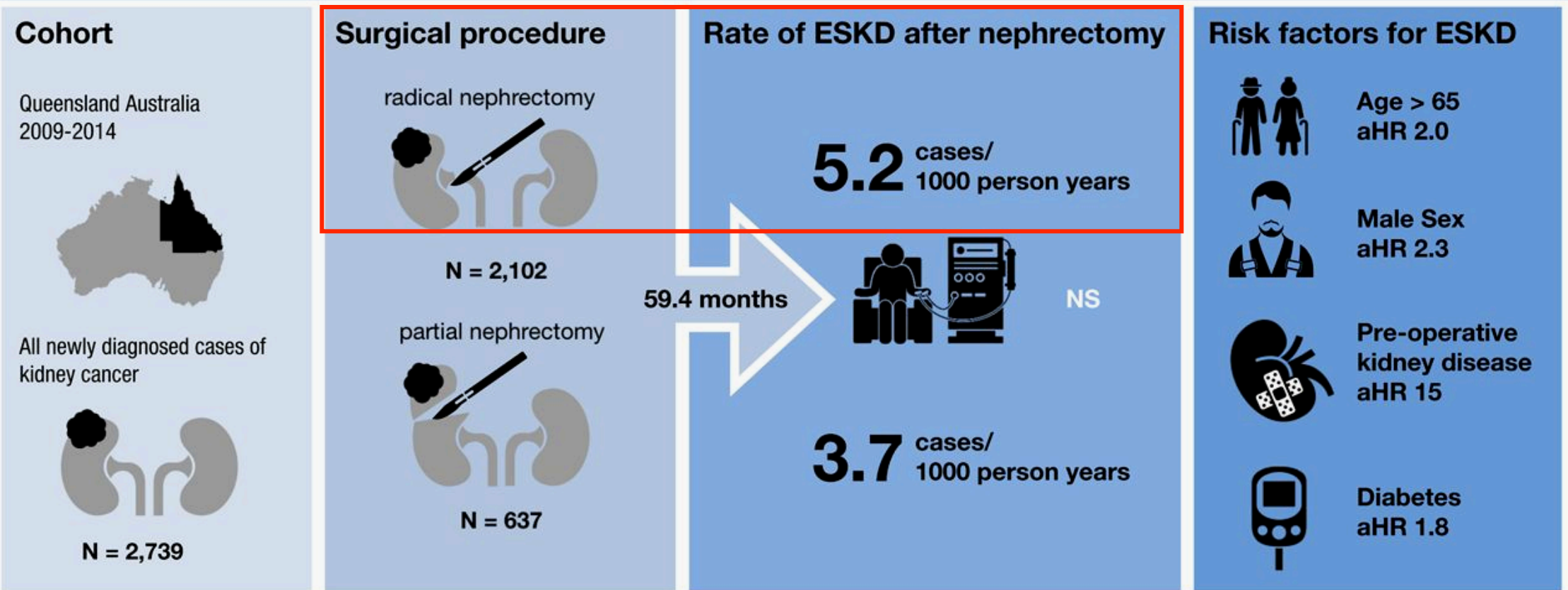
Risk Ratio and 95% CI of Incidence of Stage 3 CKD

Onco-Nephrology

ESKD in Renal Cancer

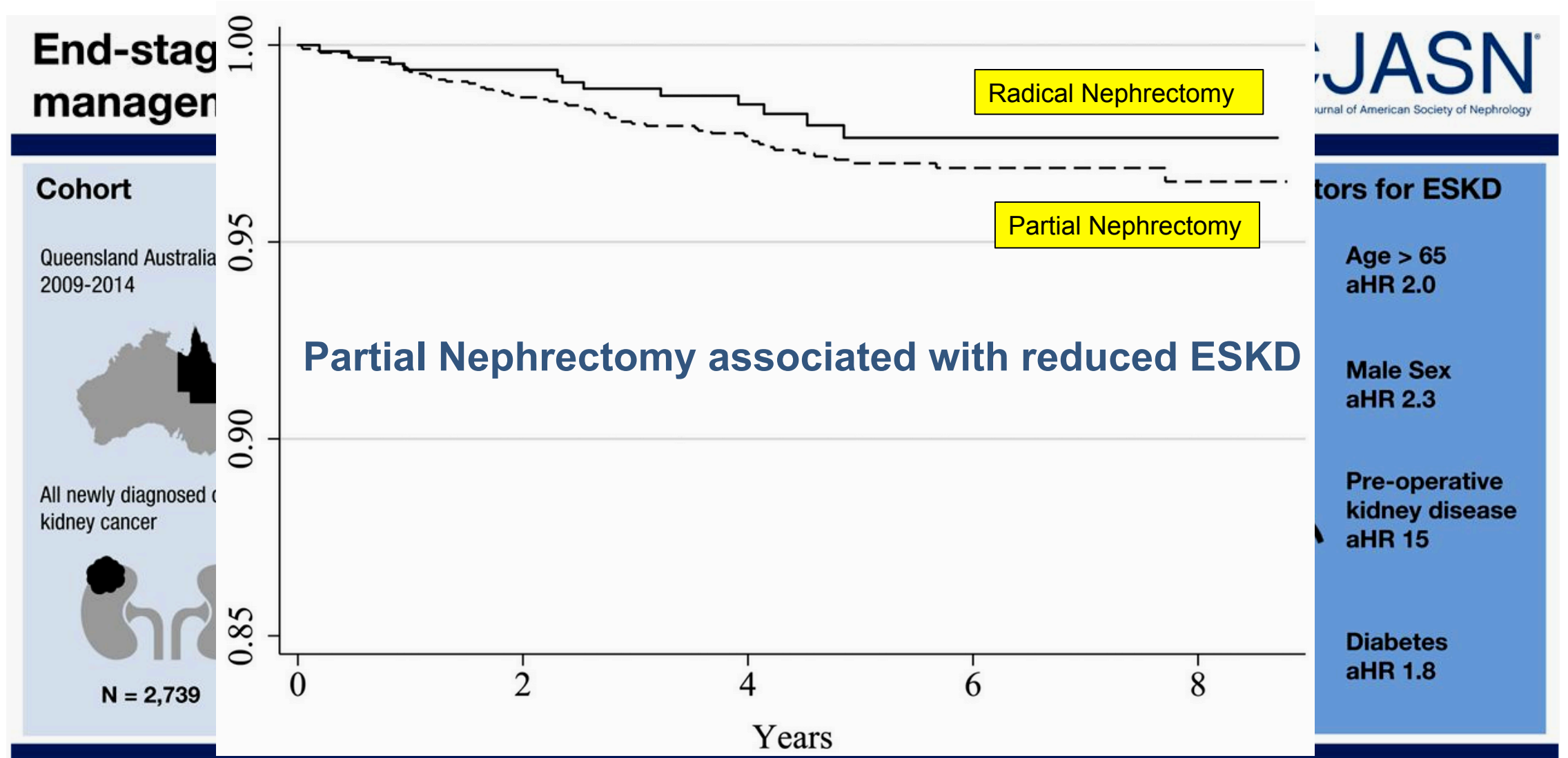
End-stage kidney disease following surgical management of kidney cancer

CJASN
Clinical Journal of American Society of Nephrology



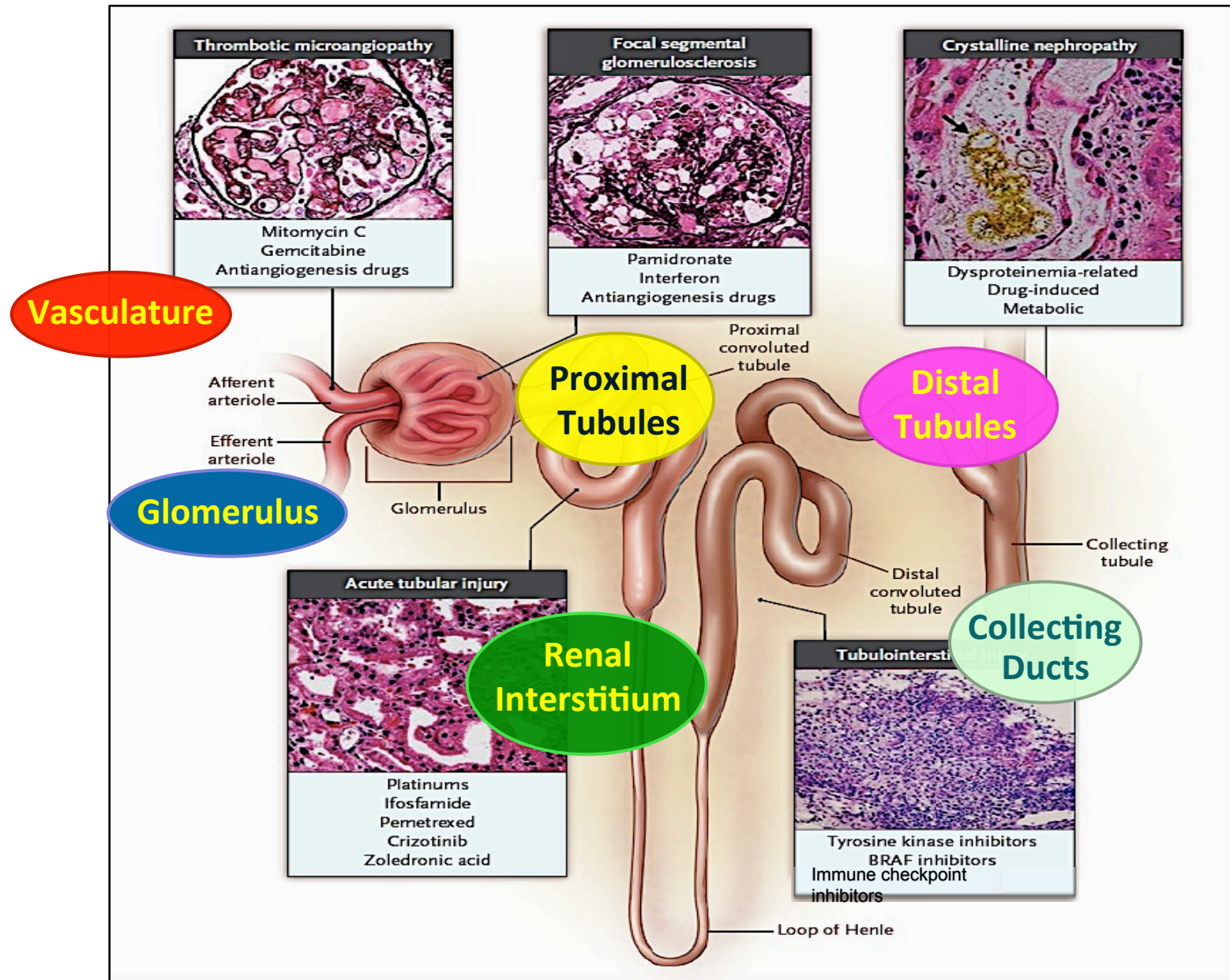
Onco-Nephrology

ESKD in Renal Cancer



Kaplan-Meier Curves for ESKD

Anti-Cancer Drug-induced Kidney Disease



Onco-Nephrology

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*
- *Proteasome inhibitors*

• Immunotherapies

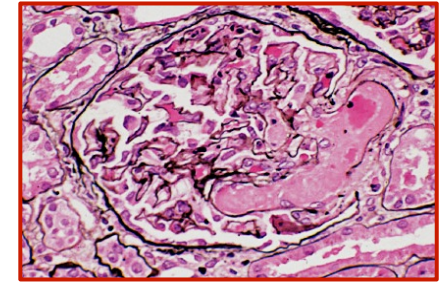
- *IL-2, interferon*
- *Immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PDL1)*
- *Chimeric antigen receptor T cells*

Conventional Chemotherapeutic Agents

Kidney Disease

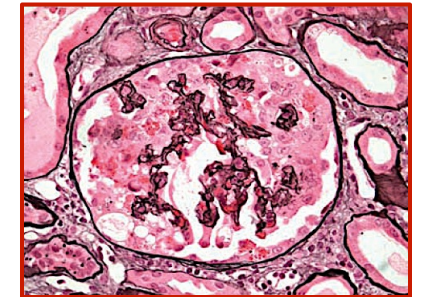
- Gemcitabine, Mitcomycin C,
Cisplatin–

TMA



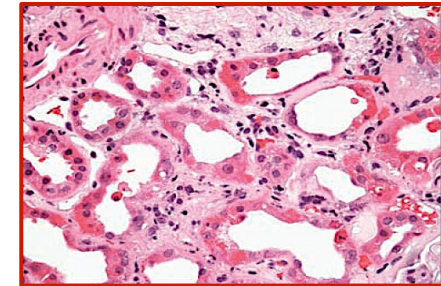
- Pamidronate–

Collapsing FSGS



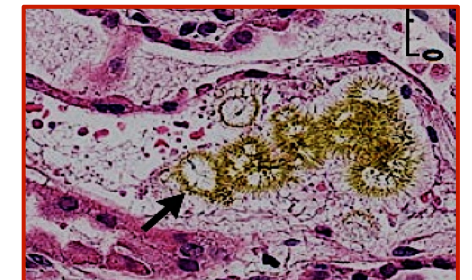
- Platins, Ifosfamide, Pemetrexed,
Zoledronate–

Toxic ATI/ATN



- Methotrexate–

Crystalline ATI

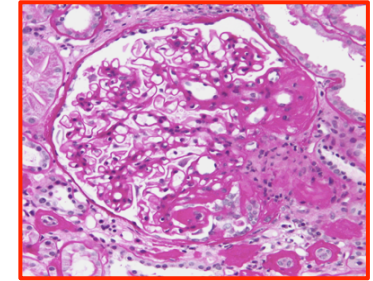
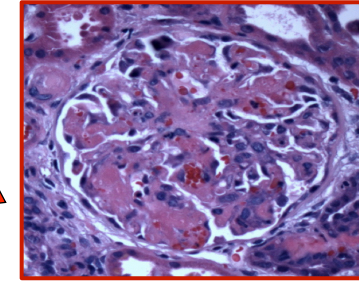


Targeted Anti-Cancer Agents

Kidney Disease

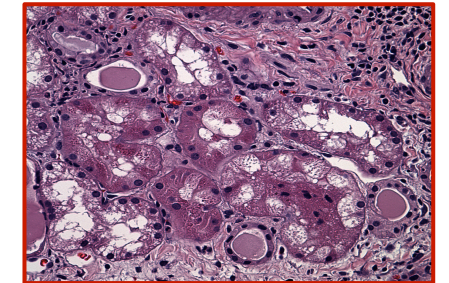
- Anti-VEGF inhibitors—

TMA, MCD/FSGS



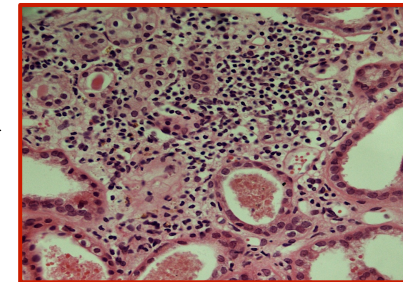
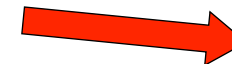
- ALK inhibitors—

**Pseudo-AKI, ATI/ATN,
Renal cysts**



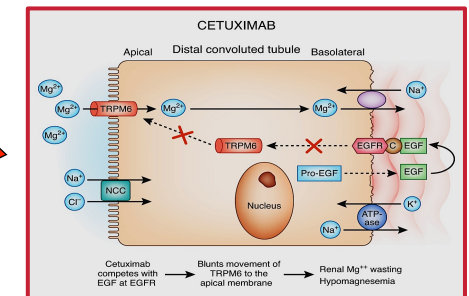
- BRAF inhibitors—

AIN/ATN



- EGFR antibodies—

Hypomagnesemia

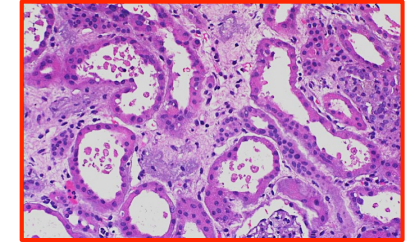
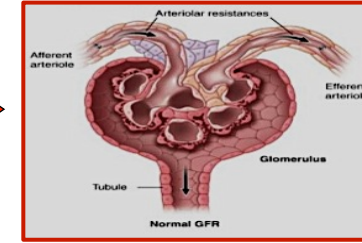


Cancer Immunotherapies

Kidney Disease

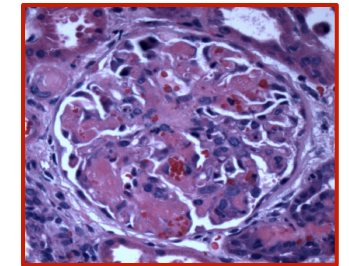
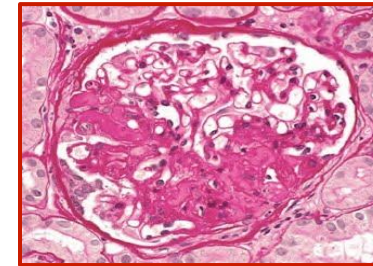
- Interleukin-2–

Prerenal AKI, ATN,
PI-GN



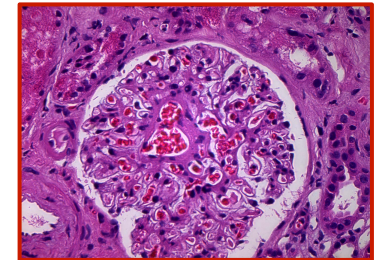
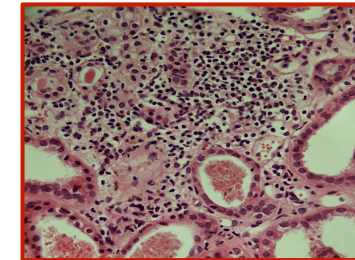
- Interferon–

FSGS/TMA



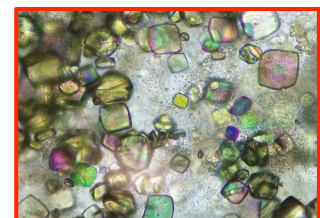
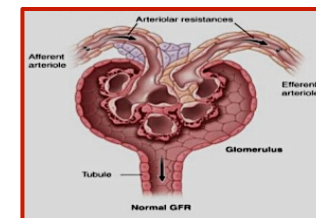
- Immune Checkpoint
Inhibitors–

AIN/IC-GN/MCD
Txp rejection



- CAR T-Cells–

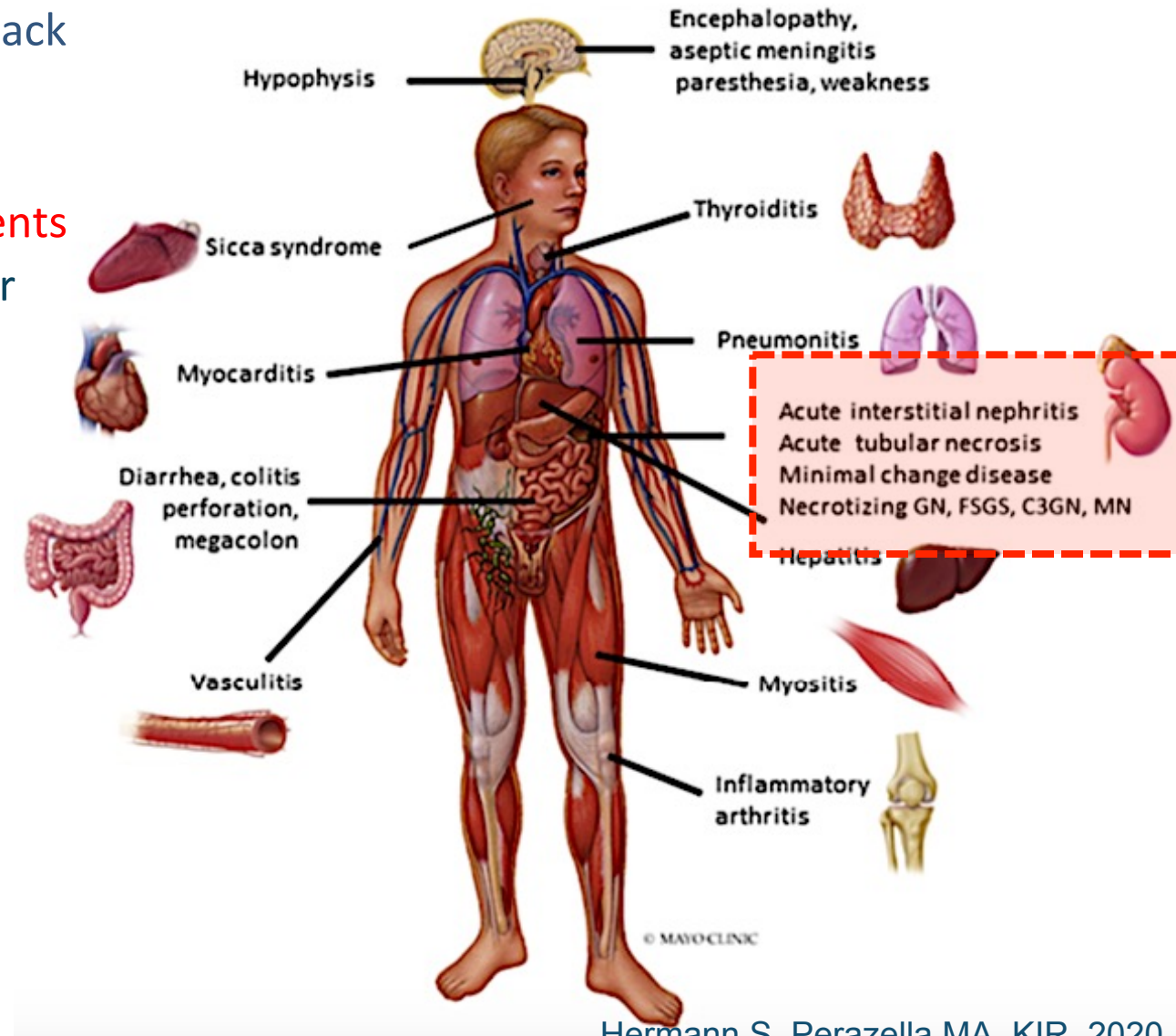
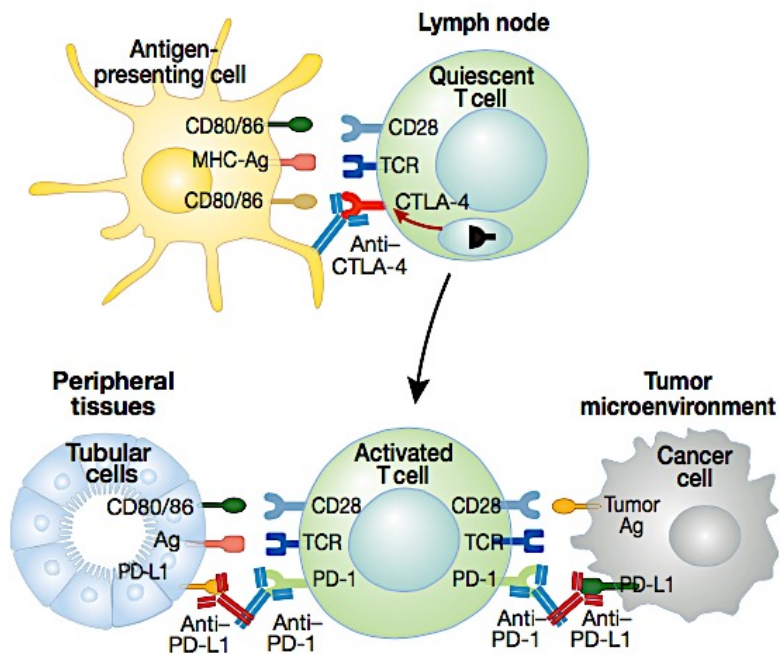
Prerenal AKI/ATI, TLS,
electrolyte disorders



Cancer Immunotherapies

Immune Checkpoint Inhibitors and Kidney Disease

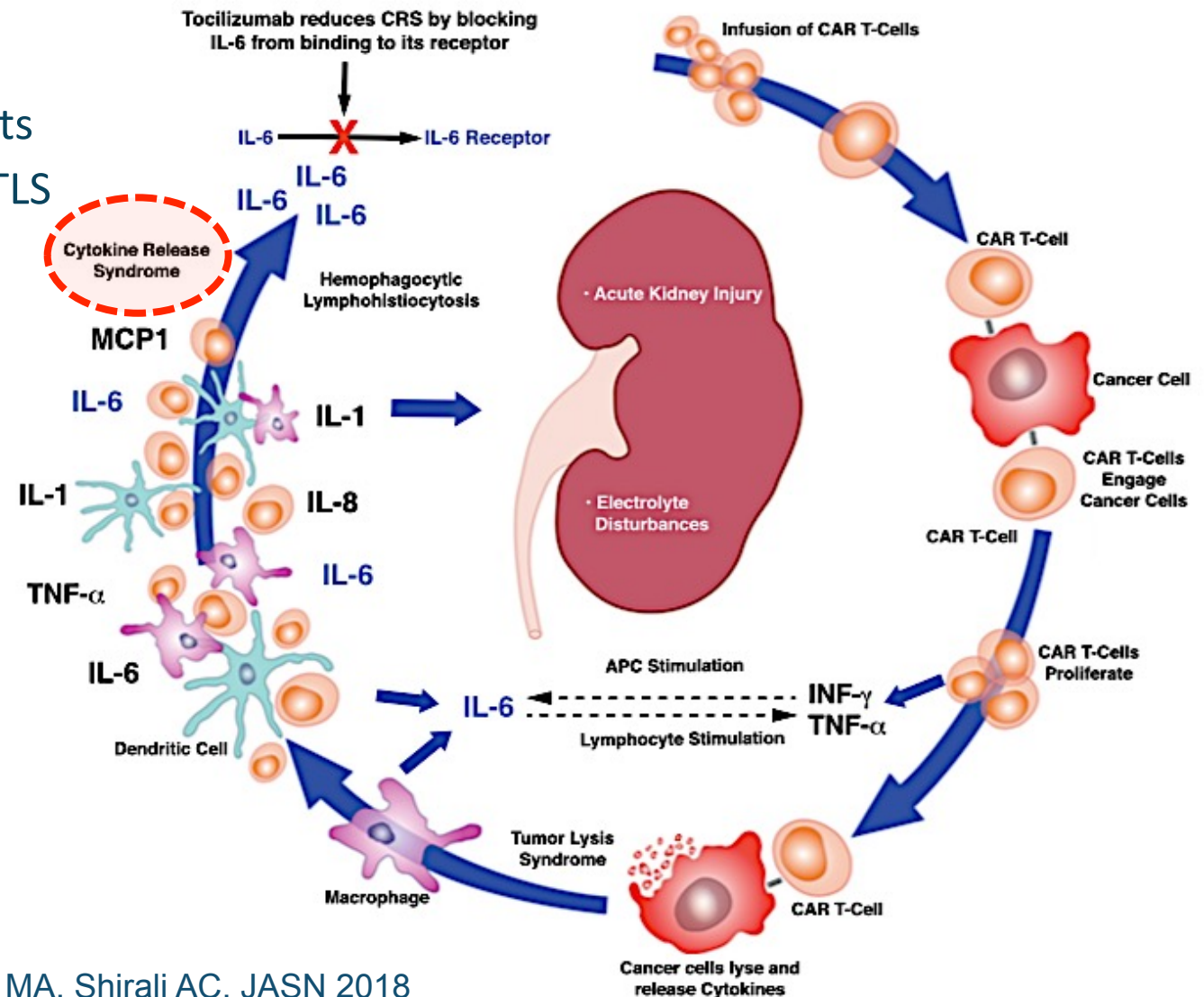
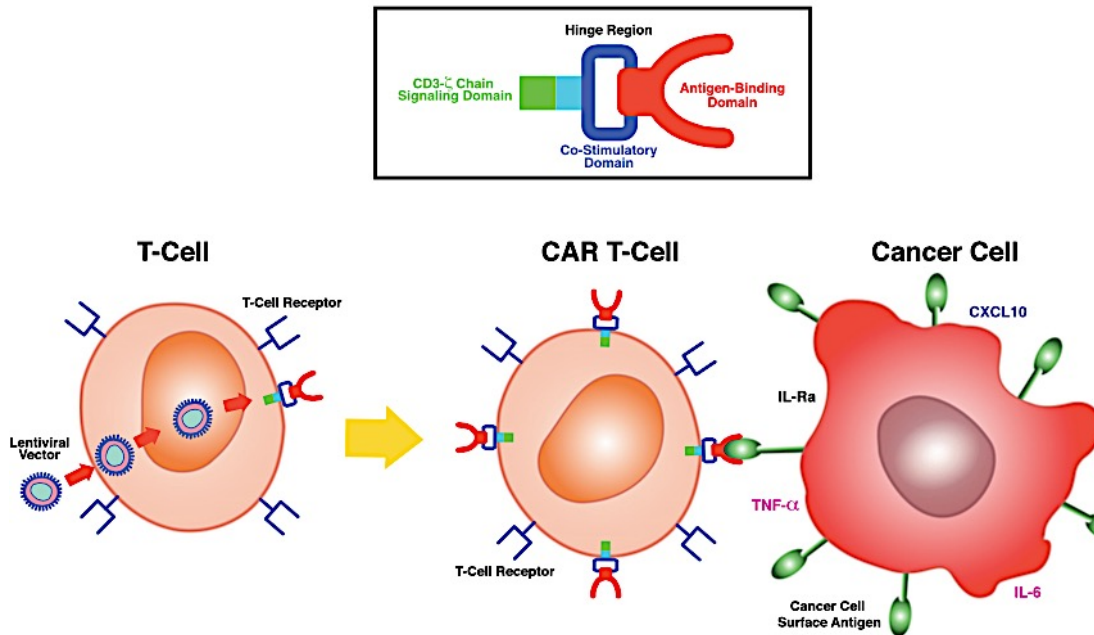
- ICPIs blunt immune checkpoints to allow T-cells to attack various cancers
- Monoclonal Abs against CTLA-4, PD-1 and PD-L1
- ICPIs are complicated by immune-related adverse events
- AKI incidence of 2-5% due primarily to ATIN, but other lesions also occur



Cancer Immunotherapies

CAR T-Cell and Kidney Disease

- 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

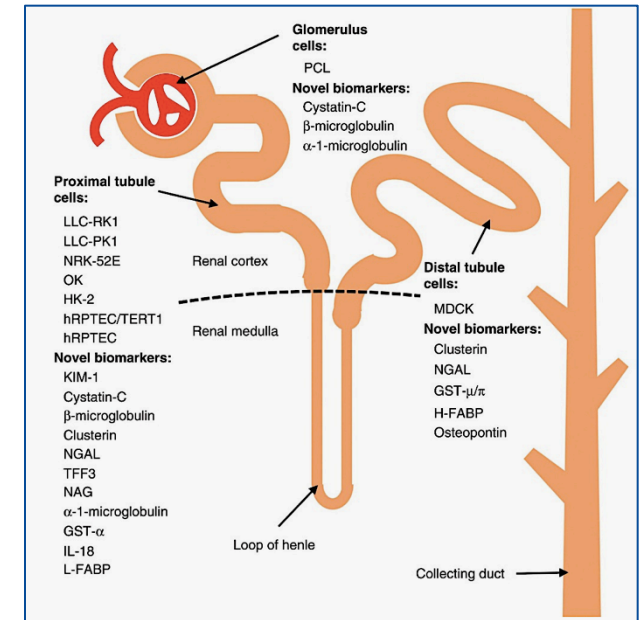
What do we need to do?

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

Onco-Nephrology

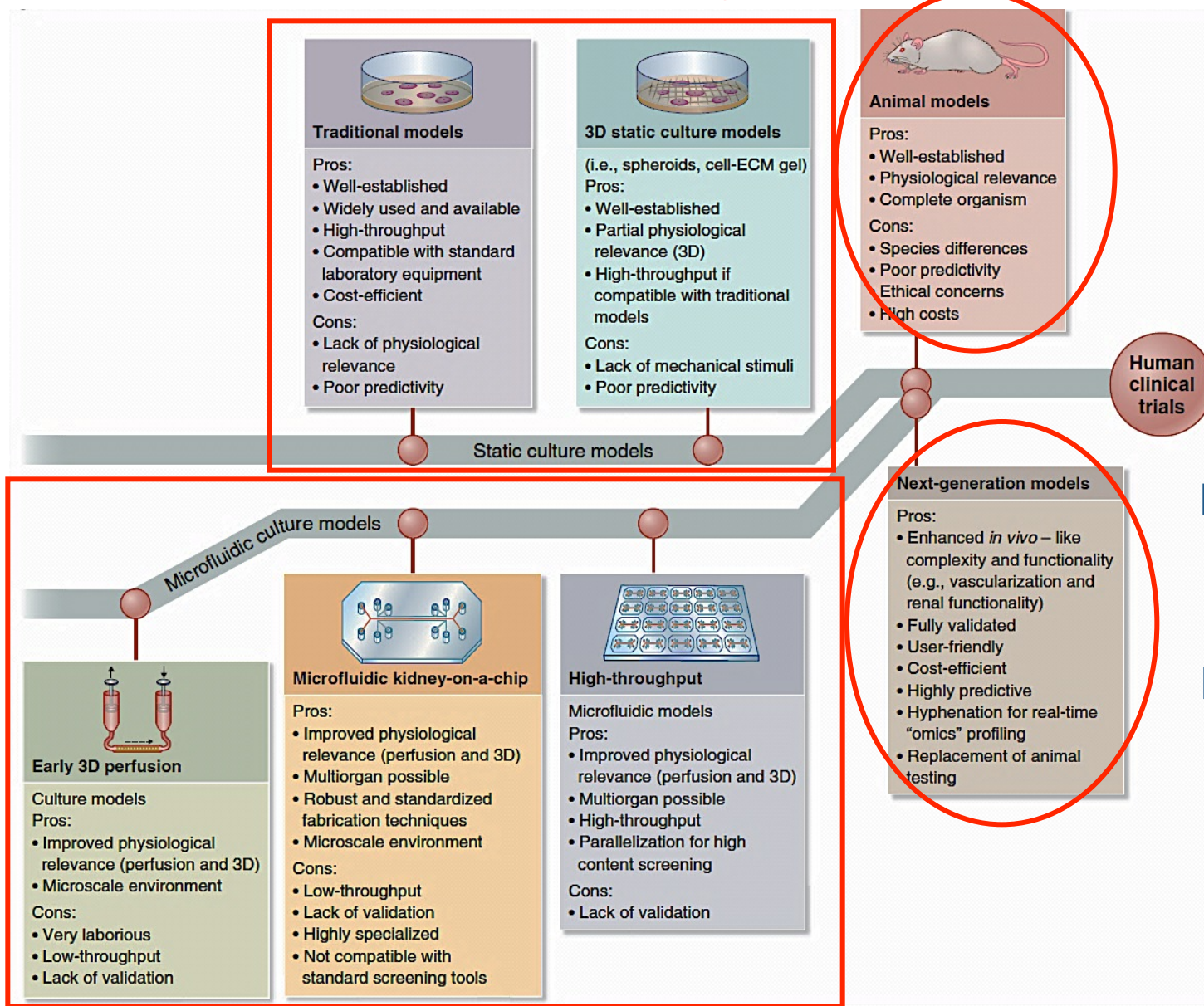
What do we need to do?

- **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**



Onco-Nephrology

Kidney on a Chip Technology



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**

Microfluiditic Culture Models

- Have Physiological Relevance
- **Laborious, Lack of Validation**

Next Generation Models

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

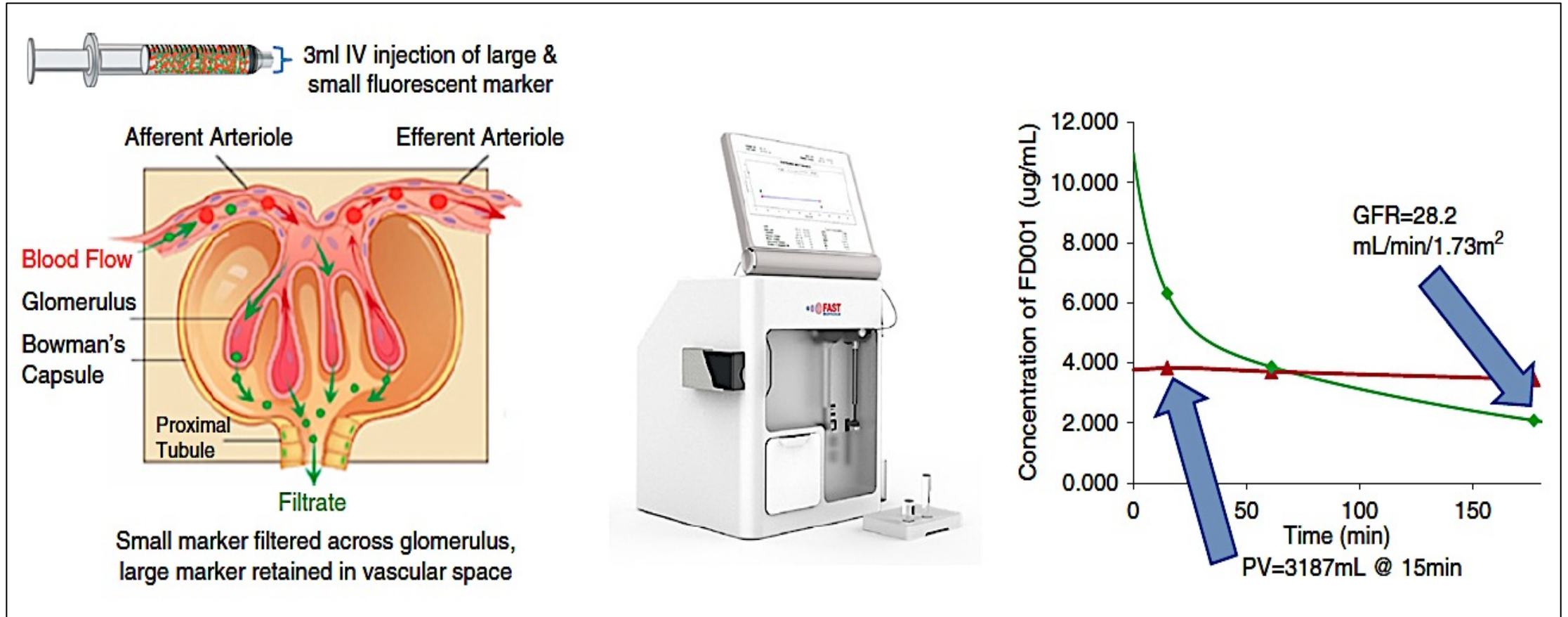
Onco-Nephrology

What do we need to do?

- **Clinical Research in Onco-Nephrology**
 - Develop better **GFR estimates** for drug dosing in cancer/CKD patients
 - 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

Onco-Nephrology

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.

Onco-Nephrology

POC tests that provide 'measured GFR'

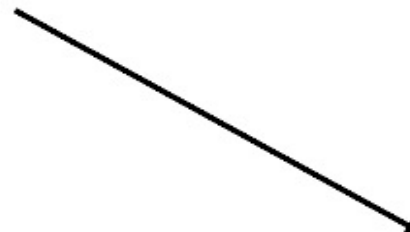
- Patented fluorescent tracer agent



Lumitrace™
(relmapirazin)

- Device

- Transdermal fluorescence detection sensor
 - LED light source
 - Photodetector
- Display monitor
 - Data acquisition software
 - GFR calculation software



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

Opening an onconeurology 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, Cezary A. Szczylik⁹ and Maurizio Gallieni^{1,10}

¹Onco-Nephrology Clinic, Nephrology and Dialysis Unit, San Carlo Borromeo Hospital, ASST Santi Carlo e Paolo, Milan, Italy, ²Medical Oncology, IRCCS San Matteo University Hospital Foundation, Pavia, Italy, ³Section of Nephrology, Department of Medicine, Yale University School of Medicine, New Haven and Veterans Administration Medical Center, West Haven, CT, USA, ⁴Service ICAR, Pitié-Salpêtrière University Hospital, Paris, France, ⁵Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA, ⁶Division of Kidney Diseases and Hypertension, Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, USA, ⁷Nephrology and Dialysis Unit, G. Brotzu Hospital, Cagliari, Italy, ⁸Nephrology Department, Centre Hospitalier Lyon Sud Pierre-Bénite, France, ⁹Department of Oncology, University of Warsaw School of Medicine, Warsaw, Poland and ¹⁰Department of Clinical and Biomedical Sciences “Luigi Sacco”, University of Milan, Milan, Italy

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

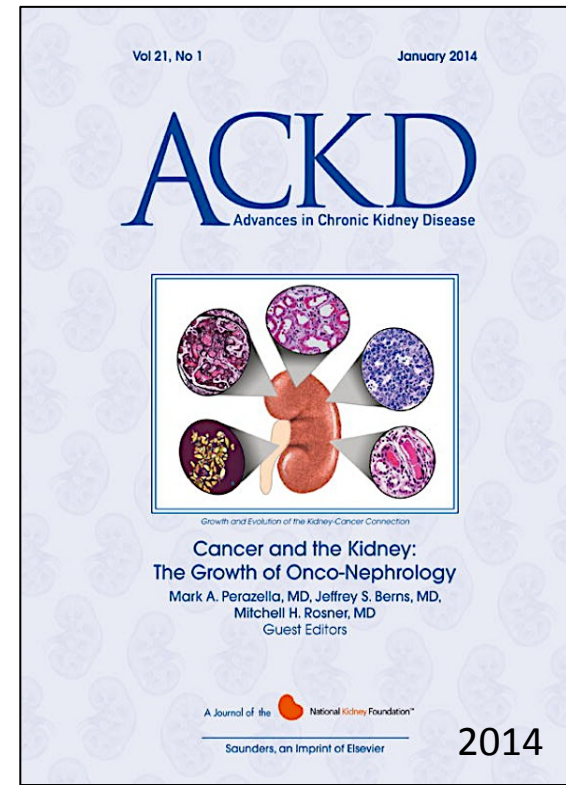
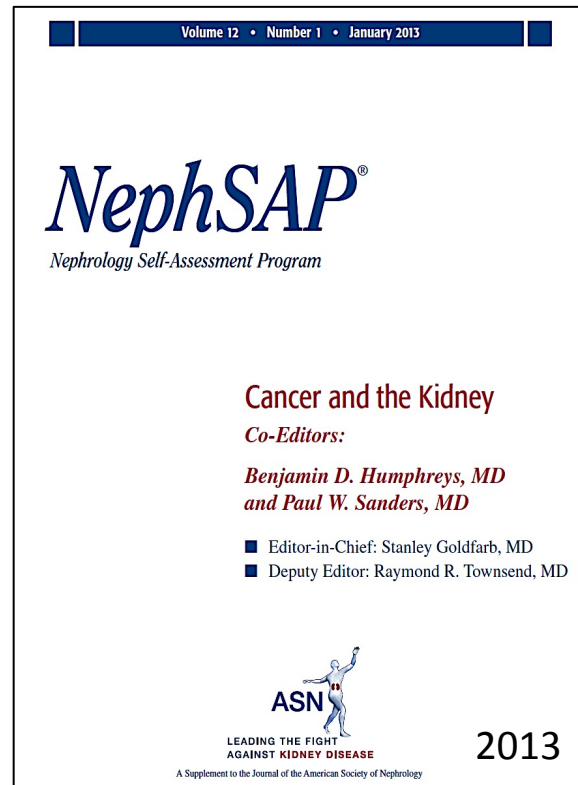
ASN Educational Curriculum-2016

Onco-Nephrology: Growth of the Kidney-Cancer Connection	1
Mark Perazella, MD, and Mitchell Rosner, MD	
Why Do We Need an Onco-Nephrology Curriculum?	2
Mark Perazella, MD, and Mitchell Rosner, MD	
AKI Associated with Malignancies	3
Amit Lahoti, MD, and Benjamin Humphreys, MD, PhD	
Tumor Lysis Syndrome	4
Amaka Edeani, MD, and Anushree Shirali, MD	
Electrolyte and Acid-Base Disorders and Cancer	5
Anushree Shirali, MD	
Glomerular Disease and Cancer	6
Divya Monga, and Kenar Jhaveri	
Hematologic Diseases and Kidney Disease	7
Ala Abudayyeh, MD, and Kevin Finkel, MD, FACP, FASN, FCCM	
Clinical tests for Monoclonal Proteins	8
Nelson Leung, MD	
Hematopoietic Stem Cell Transplant-Related Kidney Disease	9
Sangeeta Hingorani, MD, and Joseph Angelo, MD, MPH	
Radiation Nephropathy	10
Amaka Edeani, MBBS, and Eric Cohen, MD	

Chemotherapy and Kidney injury	11
Ilya Glezerman, MD, and Edgar Jaimes, MD	
Pharmacokinetics of Chemotherapeutic Agents in Kidney Disease	12
Sheron Latcha, MD, FASN	
CKD as a Complication of Cancer	13
Laura Cosmai, MD, Camillo Porta, MD, and Maurizio Gallieni, MD, FASN	
Hereditary Renal Cancer Syndromes	14
Katherine Nathanson, MD	
Work-up and Management of Small Renal Masses	15
Susie Hu, MD Anthony Chang, MD	
Cancer in Solid Organ Transplantation	16
Mona Doshi, MD	
Cancer Screening in ESRD	17
Jean Holley, MD	
Ethics of RRT, Initiation and Withdrawal, in Cancer Patients	18
Michael Germain, MD	
Palliative Care in Patients with Kidney Disease and Cancer	19
Alvin H. Moss, MD, FACP, FAAHPM	

Onco-Nephrology

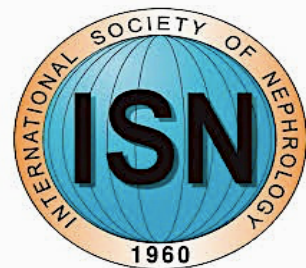
Educational Textbooks and Journals



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 Nephrological 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!