Incidentalomas: The Era of Overdiagnosis of Renal Masses

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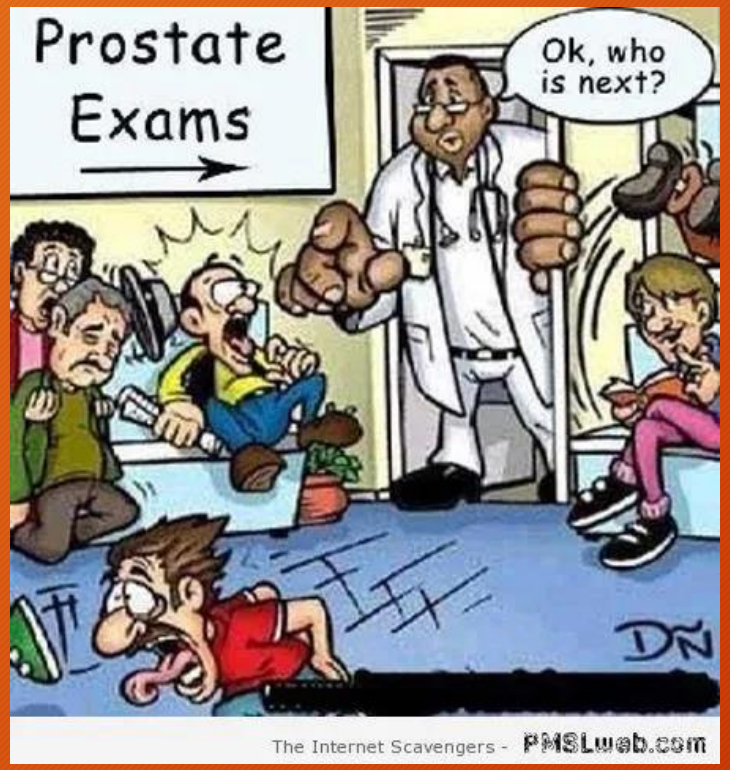

Prostate Exams
Ok, who is next?
The Internet Scavengers - PMSLweb.com


PROSTATE EXAMS
PLEASE ENTER THROUGH BACK DOOR
...OR IS DAT TOO OBVIOUS?

Outline

- Epidemiology
- Subtypes of RCC
- Clinical presentation
- Diagnosis
- Work up
- Management
- Follow up

Epidemiology

- RCC 6th most frequently diagnosed cancer in men and 10th in women
- In Europe and North America, lifetime risk of developing RCC btw 1.3% and 1.8%
- Greater than 140,000 RCC related deaths yearly
- RCC 13th most common cause of death world-wide

Epidemiology

- Arises from proximal convoluted tubule (clear cell)
- M:F ratio of 3:2
- Most cases are sporadic with only 2-3% familial
- Typical presentation btw 50-70 YOA
- Most lethal of the common urological cancers
- Higher incidence rates in AA's (more lethal also)
- Increased incidence of RCC (3-4% per year) due to increased radiologic modalities

Risk factors of RCC

- Tobacco smoking
- Obesity
- Hypertension
- Horseshoe kidney (IMA interference)
- Chronic renal failure (development of renal cysts)
- Genetic risk factors (hereditary RCC)

Benign Renal Masses

- 1. **Oncocytoma:** enhancing mass on CT(indistinguishable from RCC)
- Spoke-wheel pattern on angiography or stellate scar on CT
- No malignant transformation in sporadic cases
- Nephron-sparing surgery preferred

- 2. **Juxtaglomerular cell tumor:** more often called reninoma
- Affects women in 3rd or 4th decade
- Hypersecretion of RENIN
- Presents with HTN, hypokalemia, polydipsia, polyuria, myalgia, and headaches
- Nephron-sparing surgery favored (reverses symptoms)

Benign Renal Masses

- 3. **Leiomyoma:** arise from smooth muscle usually in capsule
- Found more often at autopsy (4-5%)
- Inconclusive from RCC on imaging
- Nephron-sparing surgery preferred

- 4. **Angiomyolipoma (AML):**
- Blood vessels, muscle, and fat
- Most common tumor associated with spontaneous perirenal hemorrhage
- 50-60% of TSC pts develop AMLs
- Pregnancy increases risks of spontaneous bleeding
- HU -20 on CT
- Can have fat-poor AML (RCC mimicker)
- Embolization paramount in bleeding
- Nephron-sparing surgery preferred surgical method

Benign Renal Masses

- 5. Cystic Nephroma:
- Bimodal age distribution (first 2-3 years of life with boys>girls, and 4th and 5th decade of life with females>males)
- Unable to discern cystic RCC from cystic nephroma radiographically (also Wilms tumor in children)
- In children- usually radical nephrectomy
- In adults- nephron-sparing preferred

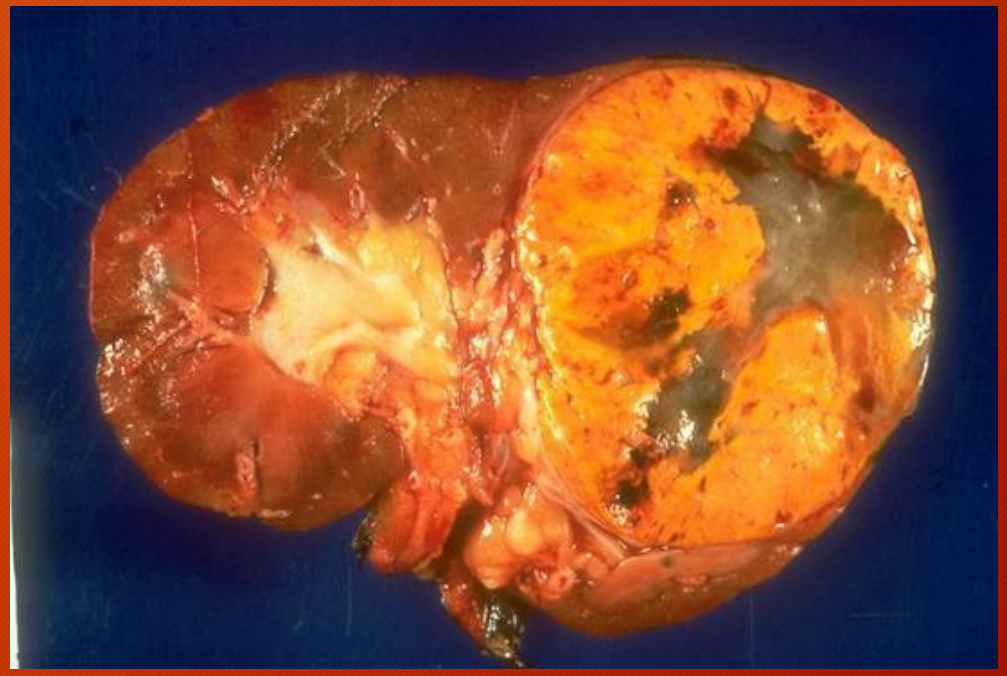
- 6. Metanephric Adenoma:
- F>M predominance
- Peak incidence in 5th decade of life
- Rare tumor and diagnosed pathologically after excision
- Percutaneous biopsy can help in diagnosis
- Most get surgical excision

Renal Cyst Disease

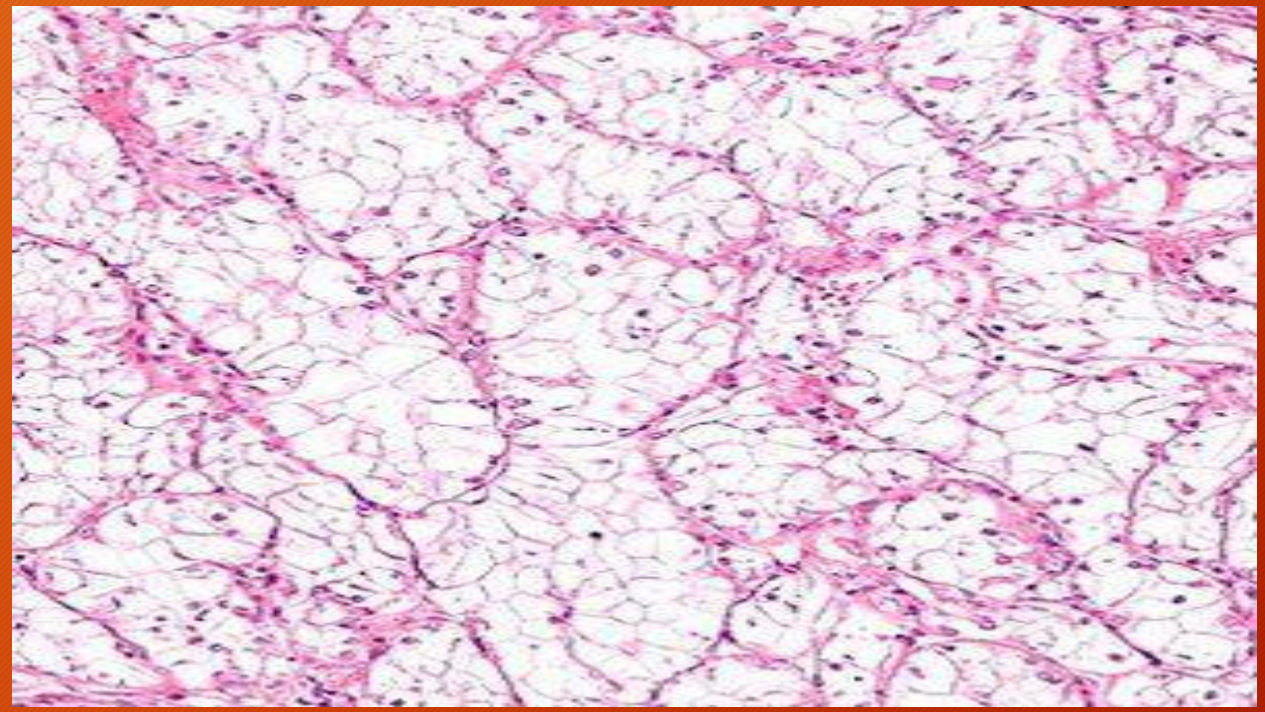
Bosniak category	Characteristics	Malignant risk (%)	Work up
Category I (uncomplicated, simple benign cyst)	Thin wall, without septations, calcifications or rigid components; homogeneous water content (<20 HU); sharp delineation with the renal parenchyma; no contrast enhancement	<1%	No follow up
Category II (minimally complex cyst)	Thin wall (< 1 mm), with fine calcifications and/or septations; < 3 cm in diameter; no contrast enhancement	<3%	No follow up
Category II F (cystic lesion with increased abnormal findings)	Slightly thick and irregular wall; multiple thin septum; presence of calcifications or dense lesions; = 3 cm in diameter; no contrast enhancement	5-10%	US/CT follow up
Category III (more complicated renal cyst)	Uniform wall thickening/nodularity; multiple thick septa; thick/irregular calcifications; contrast enhancement	40-60%	Surgical excision
Category IV (malignant cyst)	Large cystic components; irregular margins/prominent nodules; solid enhancing elements (> 10 HU), independent of septa	>80%	Surgical excision

Subtypes of RCC- Clear Cell RCC

- Clear Cell RCC (70-80% of all RCC)
- Originates from PCT
- gross section reveals yellow tissue and highly vascular
- Microscopically has clear cytoplasm
- Has worse overall prognosis than papillary or chromophobe
- Chromosome 3 alterations

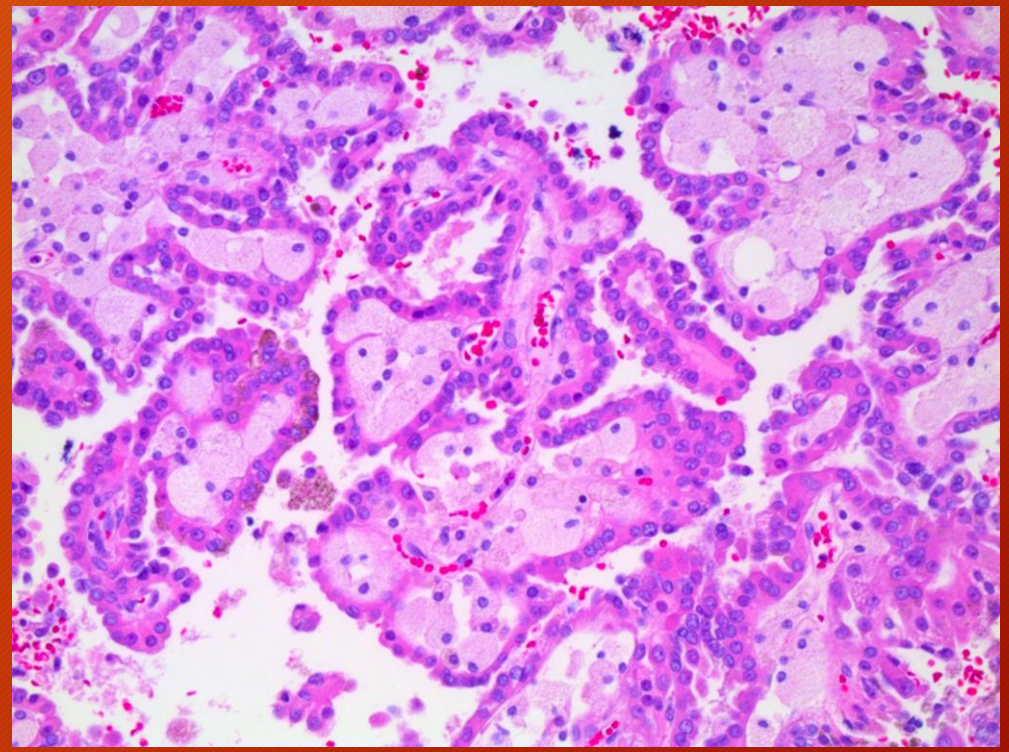


Clear Cell RCC



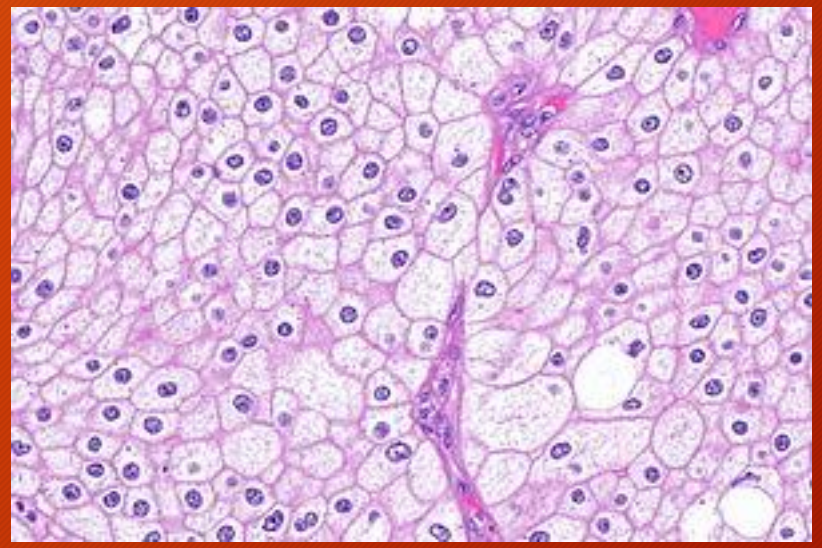
Papillary RCC

- Second most common type (10-15%)
- PCT origin
- Eosinophilic cells microscopically
- More common in ESRD pts and acquired renal cystic diseases
- Type 1 and Type 2 subtypes
- Ch 7 and 17 alterations



Chromophobe RCC

- Represents 5% of RCCs
- Derived from cortical portion of collecting duct
- Perinuclear clearing or “halo”
- Microvesicles stain positive for Hales colloidal iron
- Typically better prognosis than Clear Cell RCC



Collecting Duct RCC

- Originate from collecting ducts of Bellini (<1% of RCCs)
- Presents earlier in life with advanced stage
- Usually large infiltrative masses
- Most of unresponsive to conventional therapy
- Portends poor prognosis

Renal Medullary Carcinoma

- Occurs almost exclusively in pts with sickle cell anemia trait
- Typical in young AA pts
- Usually in 3rd decade of life
- Most cases are locally advanced and metastatic at time diagnosis
- Infiltrative near renal papillae
- Most patients die within a few months of diagnosis

Sarcomatoid Differentiation

- Found in 1-5% of RCCs
- Most associated with clear cell or chromophobe RCC
- If associated with these subtypes, usually more poorly differentiated
- Spindle cell histology, infiltrative growth pattern, aggressive local and metastatic behavior with poor prognosis

Hereditary RCC

- 1. von Hippel-Lindau Disease
- 2. Hereditary papillary RCC
- 3. Familial leiomyomatosis and RCC
- 4. Birt-Hogg Dube syndrome
- 5. Tuberous Sclerosis
- 6. Cowden syndrome

von Hippel-Lindau Disease

- Familial form of clear cell RCC
- Autosomal dominant disorder
- **Major manifestations**: clear cell RCC, pheochromocytoma, retinal angiomas, hemangioblastomas of the brainstem, cerebellum, or spinal cord
- Also can have renal and pancreatic cysts, inner ear tumors, and papillary cystadenomas of the epididymis
- Increased incidence of neuroendocrine tumors of the pancreas

VHL

- RCC develops in 50% of patients
- Early age of onset- 3rd-5th decade of life
- Bilateral and multifocal disease
- Loss of chromosome 3p (VHL tumor suppressor gene)
- VHL protein targets hypoxia-inducible factor (HIF) and when mutated HIF accumulates leading to upregulation/expression of vascular endothelial growth factor (primary angiogenic growth factor in RCC)

Familial Papillary RCC (HPRCC)

- Trisomy of Ch 7 and 17
- Autosomal dominant
- Usually type 1 papillary RCC (not type 2)
- No development of tumors of other organs
- Missense mutations of c-MET proto-oncogene at 7q 9(at tyrosine kinase domain)

Hereditary Leiomyomatosis and RCC

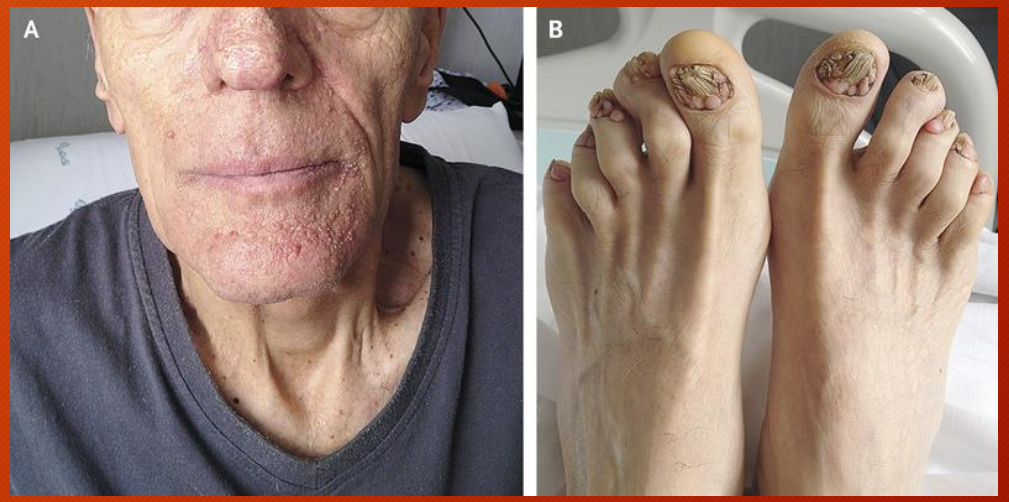
- Pts develop cutaneous and uterine leiomyomas along with type 2 papillary RCC
- Tumors are unilateral and solitary and more aggressive than other forms of familial RCC
- Disease mapped to fumarate hydratase gene (tumor suppressor gene)
- Autosomal dominant pattern (3rd decade of life)
- Only 20% develop RCC but most all develop cutaneous leiomyomas and uterine fibroids
- Prompt surgical management

Birt-Hogg-Dube Syndrome

- BHD gene- Ch 17p (autosomal dominant)
- Product of gene is tumor suppressor folliculin which interferes with mTOR pathway
- Manifestations: cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothorax and renal tumors
- Can be either chromophobe RCCs or oncocytomas
- Presents around age 50

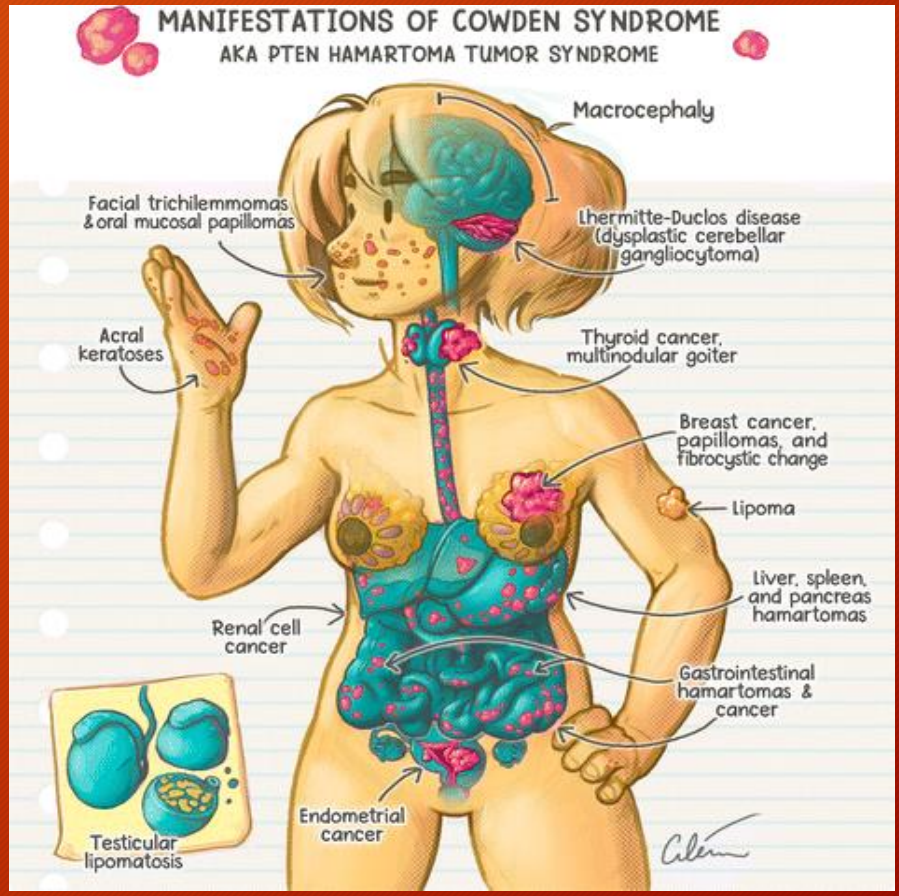
Tuberous Sclerosis

- Classic triad of mental retardation, seizures and adenoma sebaceum (30%)
- Can develop renal cysts, AML, or RCC
- 60% pts develop AMLs
- Increased risk of RCC
- Other manifestations include: ash-leaf spots (hypopigmented macules on trunk or buttocks), shagreen patches (orange-peel textured plaques on lower back), and ungual or periungual fibromas (flesh-colored papules near nail beds)



Cowden Syndrome

- Mutations of the phosphatase and tensin homolog tumor suppressor gene (PTEN)
- 50% lifetime risk of female breast cancer
- 34% lifetime risk of RCC
- 10% lifetime risk of epithelial thyroid cancer

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Clinical Presentation

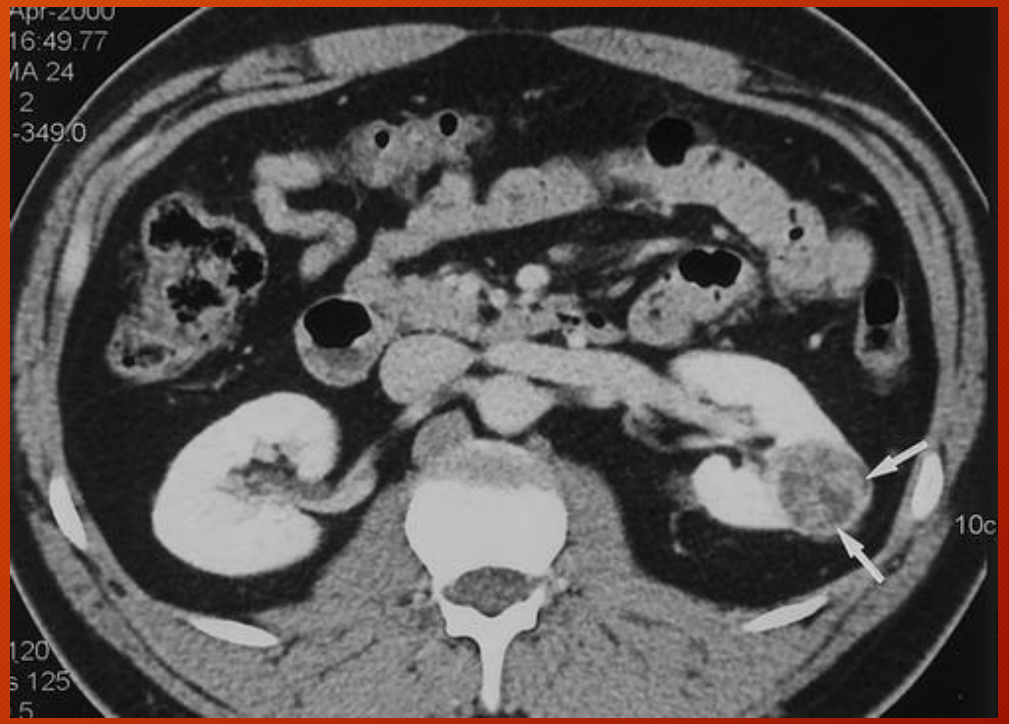
- Most are asymptomatic and non palpable
- More than 60% found incidentally
- Symptoms usually secondary to local tumor growth, hemorrhage, paraneoplastic syndromes, or metastatic disease
- Classic **triad** of flank pain, gross hematuria, and palpable abdominal mass rare
- Spontaneous perirenal hemorrhage

Paraneoplastic Syndromes Associated with Renal Cell Cancer Syndrome

	INCIDENCE (%)
Anemia	20–40
Cachexia, fatigue, weight loss	33
Fever	30
Hypertension	24
Hypercalcemia	10–15
Hepatic dysfunction (Stauffer syndrome)	3–6
Amyloidosis	3–5
Erythrocytosis	3–4
Enteropathy	3
Neuromyopathy	3

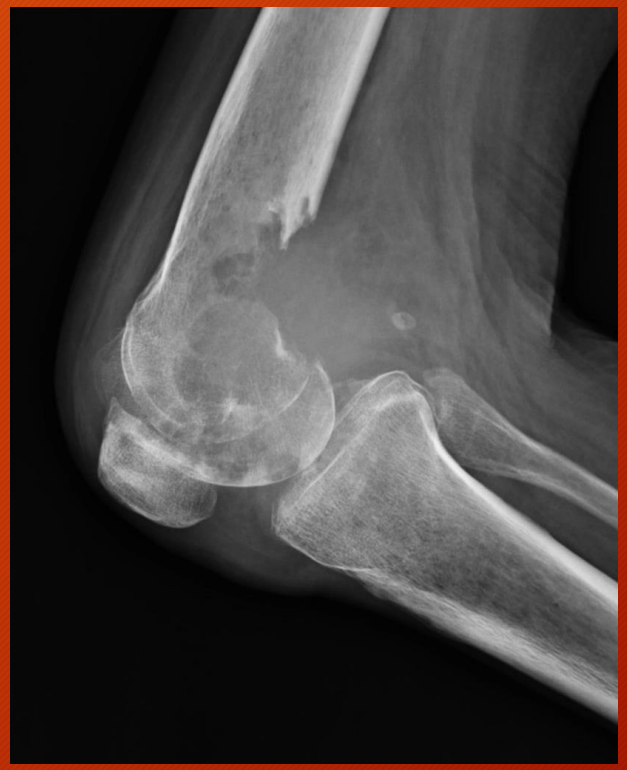
Clinical presentation

- Hematuria
- Flank pain, abdominal mass
- Perirenal hematoma (AML also)
- With IVC obstruction- RIGHT sided varicocele (B lower extremity edema)
- If systemic disease pronounced- cough, bone pain, cervical lymphadenopathy, weight loss, fever, chills



Paraneoplastic Syndrome: Hypercalcemia

- Either due to paraneoplastic syndrome or osteolytic metastatic involvement to bone
- S/S include nausea, anorexia, fatigue, decreased DTRs
- Treatments include: hydration, diuresis with furosemide, bisphosphonates, corticosteroids, or calcitonin



Paraneoplastic Syndrome: HTN

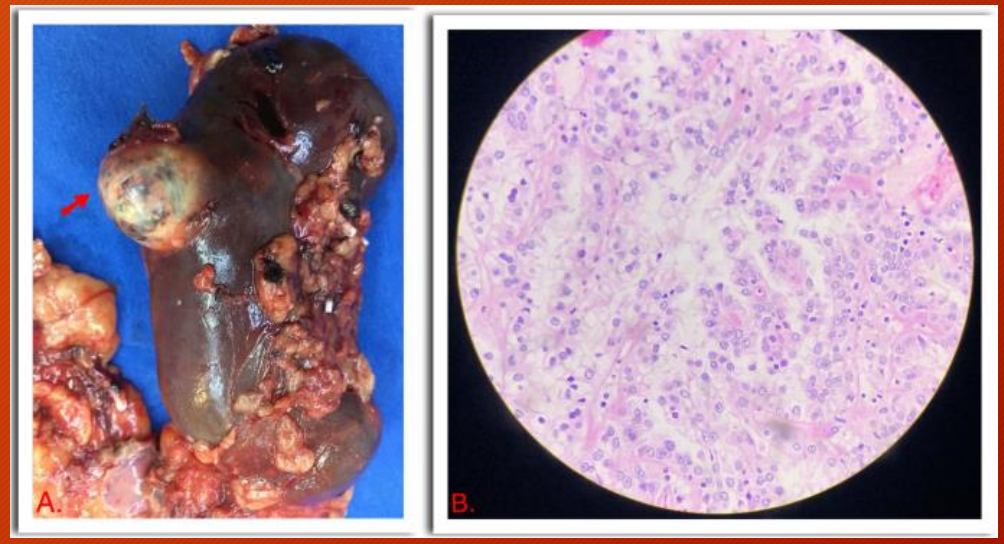
- Secondary to increased RENIN production from tumor
- Could also be secondary to compression or encasement of the renal artery or its branches
- Less common causes include polycythemia, hypercalcemia, ureteral obstruction, and increase intracranial pressure associated with cerebral mets

Paraneoplastic Syndrome: Polycythemia

- Increased production of erythropoietin
- Can be either directly from tumor or adjacent parenchyma in response to hypoxia induced by tumor growth

Paraneoplastic Syndrome: Stauffer syndrome

- Nonmetastatic hepatic dysfunction
- Elevated ALK PHOS
- 2/3 have elevated PT or hypoalbuminemia
- 1/3 have elevated bilirubin or transaminase levels
- Must rule out hepatic mets with biopsy
- Radical treatment of RCC normalizes hepatic function in 70%



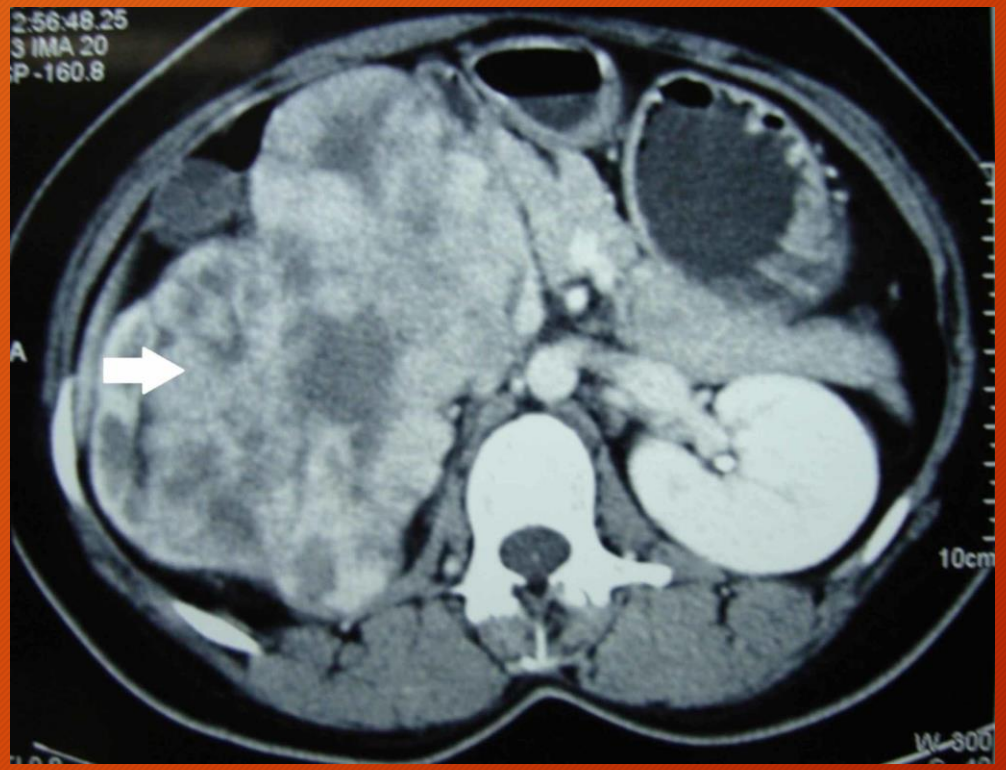
Pseudotumors

- Appear to be solid renal tumors on imaging but actually are normal renal parenchyma
- Column of Bertin, fetal lobulation, dromedary hump, nodular compensatory hypertrophy, hilar lip or uncus
- Use CT, MRI or DMSA renal scan to differentiate
- On DMSA- pseudotumors have normal isotope uptake whereas tumors have decreased uptake
- Dromedary hump- focal bulge at mid-lateral kidney (L>R) arising from downward pressure from spleen or liver development

Sarcomas of the Kidney

- 1-2% of all renal tumors
- Peak incidence in 5th decade
- Rapidly growing, large renal mass
- High grade sarcomas metastasize rapidly and portends poor prognosis
- Tumor grade and margin status most important prognostic factors
- Leiomyosarcoma most common subtype (50-60%)
- Other examples include: Liposarcoma (adipose tissue), Osteogenic sarcoma (“rock hard” and contains calcium), rhabdomyosarcoma, fibrosarcoma, carcinosarcoma, malignant fibrous histiocytoma, synovial sarcoma, schwannoma, angiosarcoma, and malignant hemangiopericytoma

Renal Leiomyosarcoma

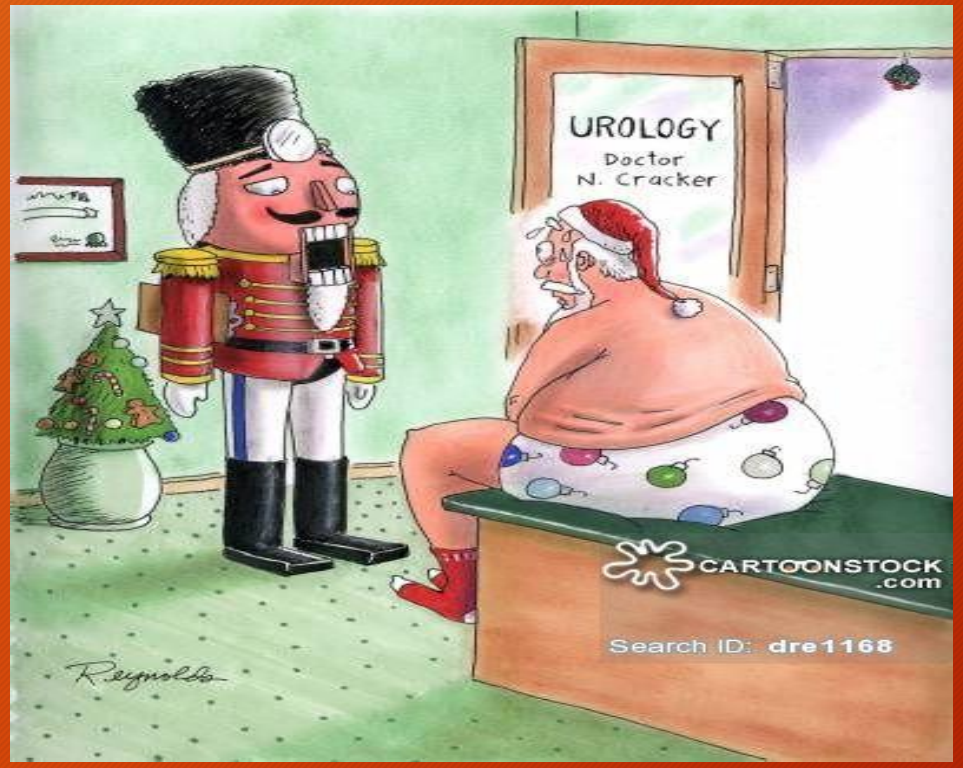


Renal Lymphoma and Leukemia

- Renal involvement with hematologic malignancies very common (found at autopsy in roughly 34% of patients dying from lymphoma or leukemia)
- Suspect in patients with massive RP LN, splenomegaly, or lymphadenopathy in other regions of the body
- Lymphomas more common in patients with iatrogenic immunosuppression, acquired immunodeficiency syndrome, autoimmune diseases, or graft-versus-host disease, and those with h/o radiation therapy
- Renal involvement related to leukemia more common in children
- If suspected, consider renal biopsy for diagnosis
- Commonly silent but can be associated with hematuria, flank pain, or progressive renal failure
- Fever, weight loss, and fatigue (B-symptoms of lymphoma) much more common
- Standard treatment is systemic chemotherapy +/- radiation (avoid any extirpative surgery)

Metastatic Tumors

- Most common malignant neoplasms in the kidney (profuse vascularity of the kidney)
- Most develop through hematogenous spread
- Most frequent sources of renal mets include lung, breast, GI cancers, malignant melanoma, and the hematologic malignant neoplasms
- Typical pattern consists of multiple small nodules that are usually clinically silent
- Suspect in any patient with multiple renal lesions and widespread systemic metastasis or any history of nonrenal primary cancer
- Utilize percutaneous biopsy for pathologic diagnosis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Work Up for suspected renal mass

- 3-D imaging (CT without and with IV contrast imaging of choice)
- History and physical exam paramount
- CBC, CMP, urinalysis (alk phos to rule out bone mets)
- Chest Xray or CT chest to rule out pulmonary mets
- Bone scan if elevated serum calcium or alk phos
- MRI brain if any neurological symptoms present
- Can get renal scan if CKD present to determine optimal treatment

TNM Staging of RCC

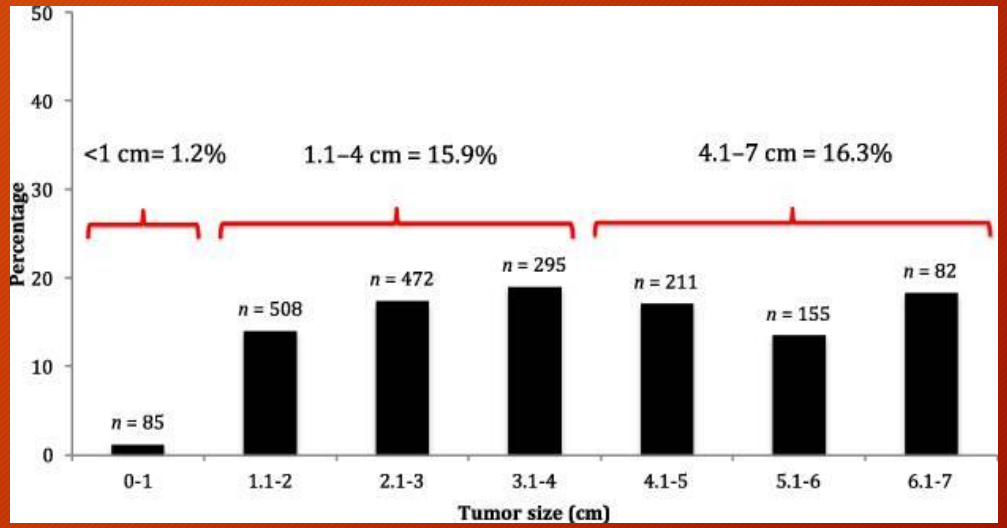
Stage	Definition	Subdivision
Tumor stage		
T0	No evidence of primary tumor	
T1	< 7 cm in greatest dimension, confined to the kidney	1a: < 4 cm (►**Fig. 1**) 1b: > 4 cm and < 7 cm
T2	> 7 cm in greatest dimension, confined to the kidney	2a: > 7 cm < 10 cm (►**Fig. 2**) 2b: > 10 cm
T3	Extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland or beyond Gerota fascia	3a: Tumor extends into renal vein branches, or invades perirenal and/or renal sinus fat (►**Fig. 3**)
		3b: Tumor extends into the subdiaphragmatic inferior vena cava
		3c: Tumor extends into the supradiaphragmatic inferior vena cava
T4	Tumor invades beyond the Gerota fascia and/or contiguous extension into the ipsilateral adrenal gland (►**Figs. 4** and **5**)	
Regional lymph nodes		
N0	No regional lymph node metastasis	
N1	Metastasis to regional lymph nodes	
Distant metastasis		
M0	No distant metastasis	

Role of Renal Mass Biopsy

- Considered when suspicion of metastatic lesion, inflammatory, infectious, lymphoma, AML
- Can confirm tumor biopsy prior to initiating systemic therapy
- Non diagnostic in 15-20% cases
- Side effects: bleeding or infection, tumor spread along biopsy tract
- Posterior tumors more likely to be biopsied compared to anterior tumors

MUSIC-KIDNEY Study

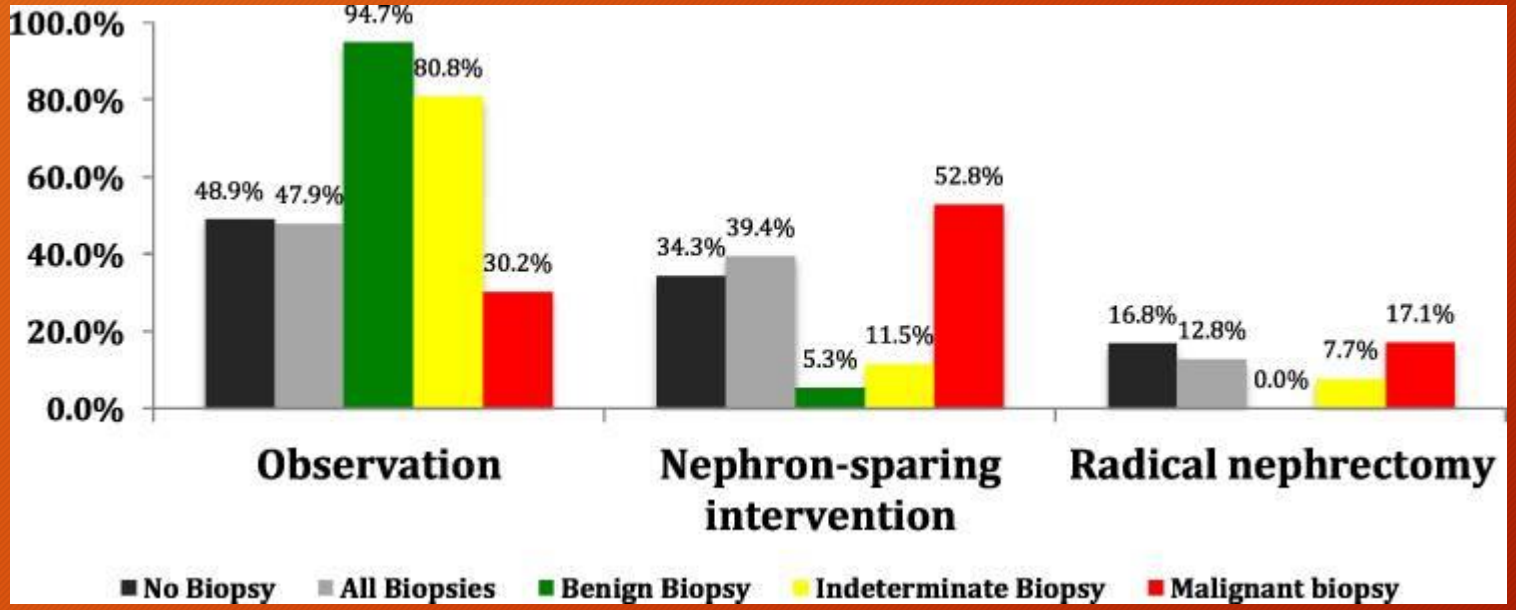
- MUSIC-KIDNEY commenced data collection in September 2017 for all newly presenting patients with a cT1 RM at 14 diverse practices. Patients were assessed at ≥120 d after initial evaluation.
- Among 1808 patients with a cT1 RM, 282 (15.5%) underwent RMB to assist in management.



MUSIC-KIDNEY Study

- Predictors of RMB included: posterior tumor location, increased comorbidities, tumor type, academic setting, higher BMI
- Rate of RMB utilization was 17.9% for solid masses, 10.3% for indeterminate lesions, and 3.5% for Bosniak III/IV cysts
- RMB before treatment for cT1 RMs include 70.6% with malignant pathology, 20.6% with benign pathology, and 9.8% with indeterminate results
- Sensitivity and specificity of RMB were 98.1% and 60.0%, respectively, for the 119 patients undergoing surgical treatment
- 5 patients with indeterminate results on RMB underwent surgical intervention, 4 with RCC and 1 patient with benign histology
- 2 patients were classified as having malignant disease at RMB (oncocytic neoplasm favoring chromophobe RCC) but pathology at surgery revealed benign (oncocytoma) findings
- 4 patients with benign RMB histology who underwent surgery all had confirmation of oncocytoma on final surgical pathology

MUSIC-KIDNEY Study

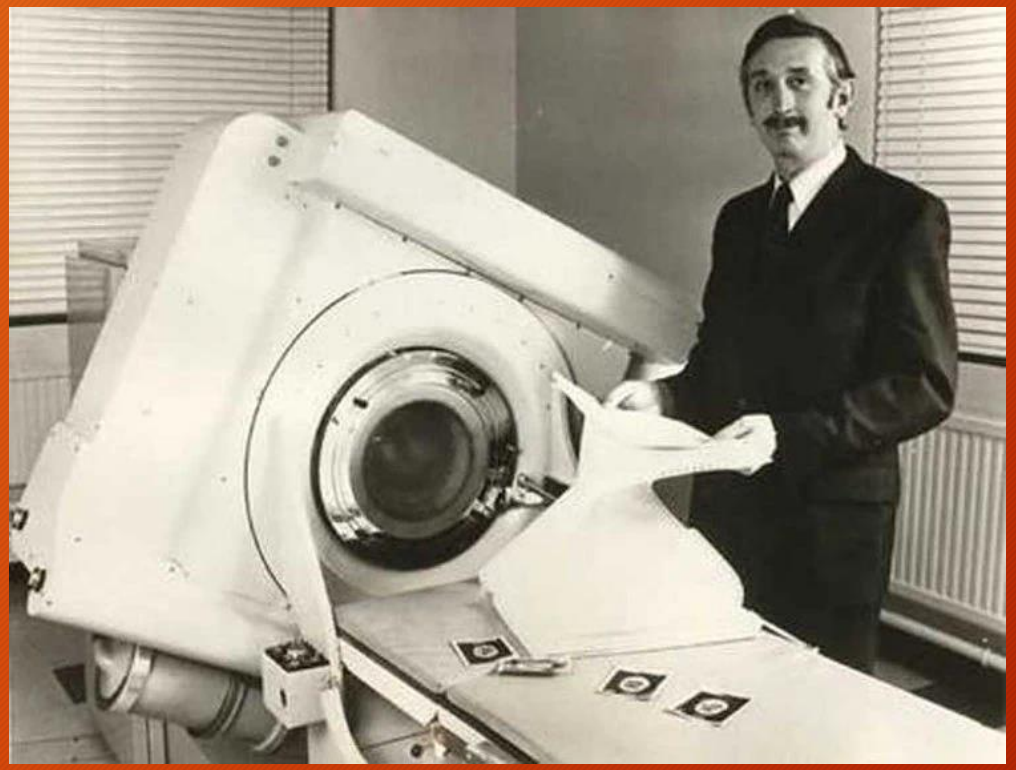


When you laugh at the possibility of a large-scale nuclear war but you have already seen the horrors of radiation exposure

History of Computed Tomography

- Tomography is from Greek word "***tomos***" meaning slice or section and "***graphia***" meaning describing
- Invented in 1972 by British engineer Godfrey Hounsfield of EMI Laboratories, England and by South Africa-born physicist Allan Cormack of Tufts University, MA
- Both later were jointly awarded 1972 Nobel Prize in Physiology and Medicine
- By 1981, Hounsfield was knighted and became Sir Godfrey Hounsfield
- However, it was the mathematical theory of Johann Radon in 1917, called "Radon transform," that brought the technology to life
- Another mathematical advancement that Hounsfield built on is the "Algebraic Reconstruction Technique," which was formulated by Polish mathematician Stefan Kaczmarz in 1937

History of Computed Tomography



History of Computed Tomography

- First patient brain CT performed in Wimbledon, England in 1971 but not publicized until a year later
- Widely rumored that the Beatles record sales in the 1960's helped fund the first CT scans development
- In 1973 the first CT scanners were installed in the U.S.
- By 1980, 3 million CT scans performed and by 2005 that number increased to 68 million scans annually
- Initial CT scans took several hours to acquire the raw data from a single slice or "section" and took several days to reconstruct a single image from this raw data
- The latest multi-slice CT systems can collect up to 4 slices of data in about 350 ms and reconstruct a 512 x 512-matrix image from millions of data points in less than a second

Computed Tomography in Pediatrics

- Pediatric Computed Tomography and Associated Radiation Exposure and Estimated Cancer Risk
- Diana L. Miglioretti, PhD, Eric Johnson, MS, Andrew Williams, PhD, Robert T. Greenlee, PhD, MPH, Sheila Weinmann, PhD, MPH, Leif I. Solberg, MD, Heather Spencer Feigelson, PhD, MPH, Douglas Roblin, PhD, Michael J. Flynn, PhD, Nicholas Vanneman, MA, and Rebecca Smith-Bindman, MD

  JAMA Pediatr. 2013 Aug 1; 167(8): 700–707.

Females: breast, thyroid, lung, and leukemia accounted for majority of cancers (68%)

Males: brain, lung, colon, and leukemia (51%)

Computed Tomography in Pediatrics

Age (years)	Head CT			Abdomen/Pelvis CT			Chest CT			Spine CT		
			Solid Cancer			Solid Cancer			Solid Cancer			Solid Cancer
	Girls	Boys	Leukemia	Girls	Boys	Leukemia	Girls	Boys	Leukemia	Girls	Boys	Leukemia
Lifetime attributable risk of cancer per 10,000 CTs												
<5	17.5	7.4	1.9	33.9	14.8	0.8	28.4	8.4	0.6	37.5	5.3	0.7
5-9	1.6	2.4	0.9	25.8	13.7	0.7	30.5	9.2	0.5	26.2	7.9	0.4
10-14	1.1	2.1	0.5	27.2	13.1	1.0	20.9	6.1	0.4	12.5	8.6	0.5
Number of CTs leading to one cancer case (rounded to the nearest 10)												
<5	570	1350	5250	300	670	12,170	350	1190	17,470	270	1890	14,630
5-9	6130	4150	11,660	390	730	14,470	330	1080	20,570	380	1260	26,940
10-14	9020	4660	21,160	370	760	10,380	480	1650	25,430	800	1170	22,020

Computed Tomography in Pediatrics

CT type	Estimated number of pediatric CTs in US (millions)	Projected number of future radiation-induced cancers related to pediatric CT use								
		Scenario 1: Doses reflect observed doses			*Scenario 2: Reduce number of exams by one third*			*Scenario 3: Doses above 75th percentile lowered to median*		
		Solid cancers	Leukemia cases	Total cancers (95% UL)	Solid cancers	Leukemia cases	Total cancers (95% UL)	Solid cancers	Leukemia cases	Total cancers (95% UL)
Head	2.2	1000	210	1210 (630, 2370)	670	140	810 (420, 1580)	470	160	630 (320, 1280)
Abdomen/Pelvis	1.4	2810	110	2930 (1600, 5360)	1880	80	1950 (1070, 3600)	1660	70	1730 (950, 3180)
Chest	0.2	340	10	350 (190, 640)	230	10	230 (130, 440)	200	10	210 (110, 390)
Spine	0.2	370	10	390 (210, 690)	250	10	260 (140, 480)	210	10	210 (120, 410)
Total	**4.0**	**4530**	**340**	**4870 (2640, 9080)**	**3020**	**230**	**3250 (1760, 6060)**	**2540**	**240**	**2780 (1500, 5220)**

Computed Tomography

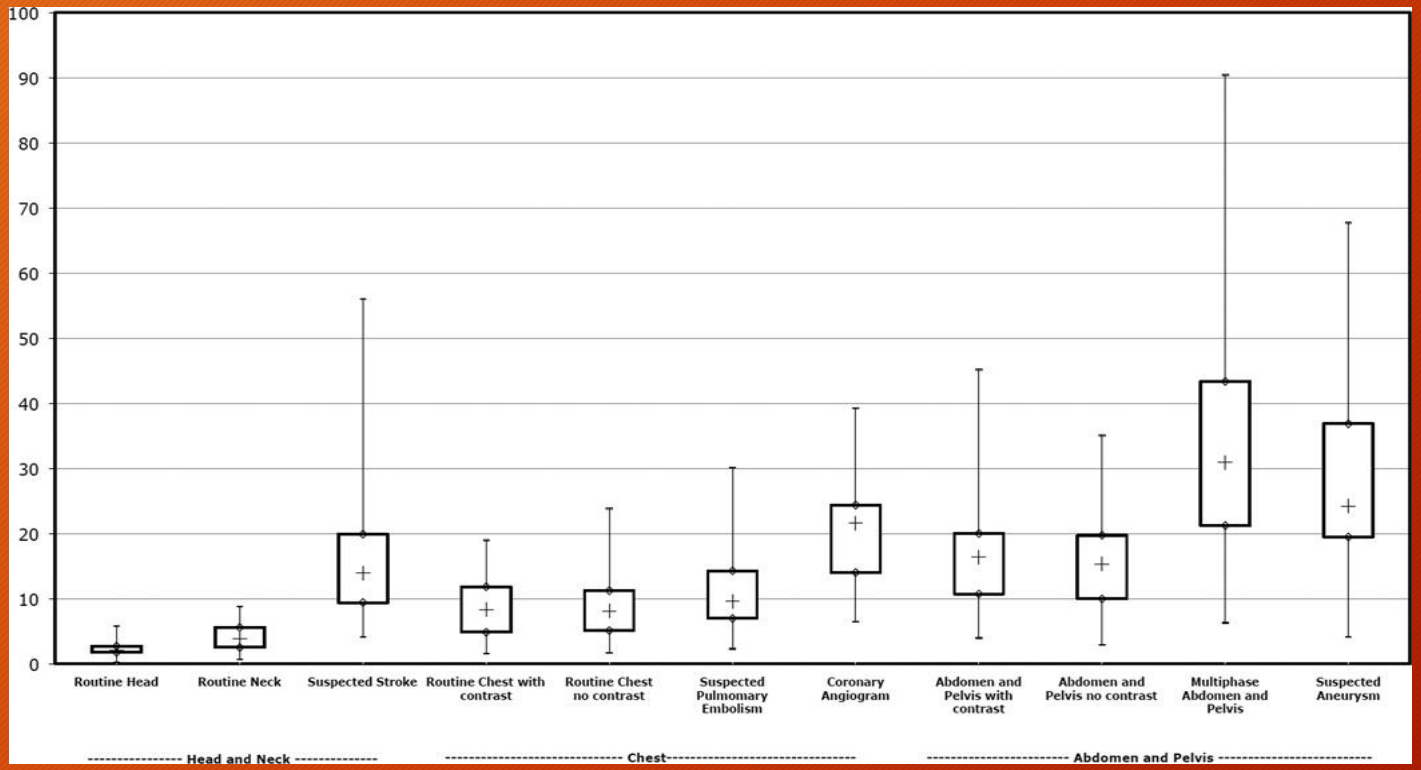
- Radiation Dose Associated with Common Computed Tomography Examinations and the Associated Lifetime Attributable Risk of Cancer

- Rebecca Smith-Bindman, MD,Jafi Lipson, MD, Ralph Marcus, BA,Kwang Pyo Kim, PhD, Mahadevappa Mahesh, MS, PhD, Robert Gould, ScD, Amy Berrington de Gonzalez, DPhil, and Diana L. Miglioretti, PhD

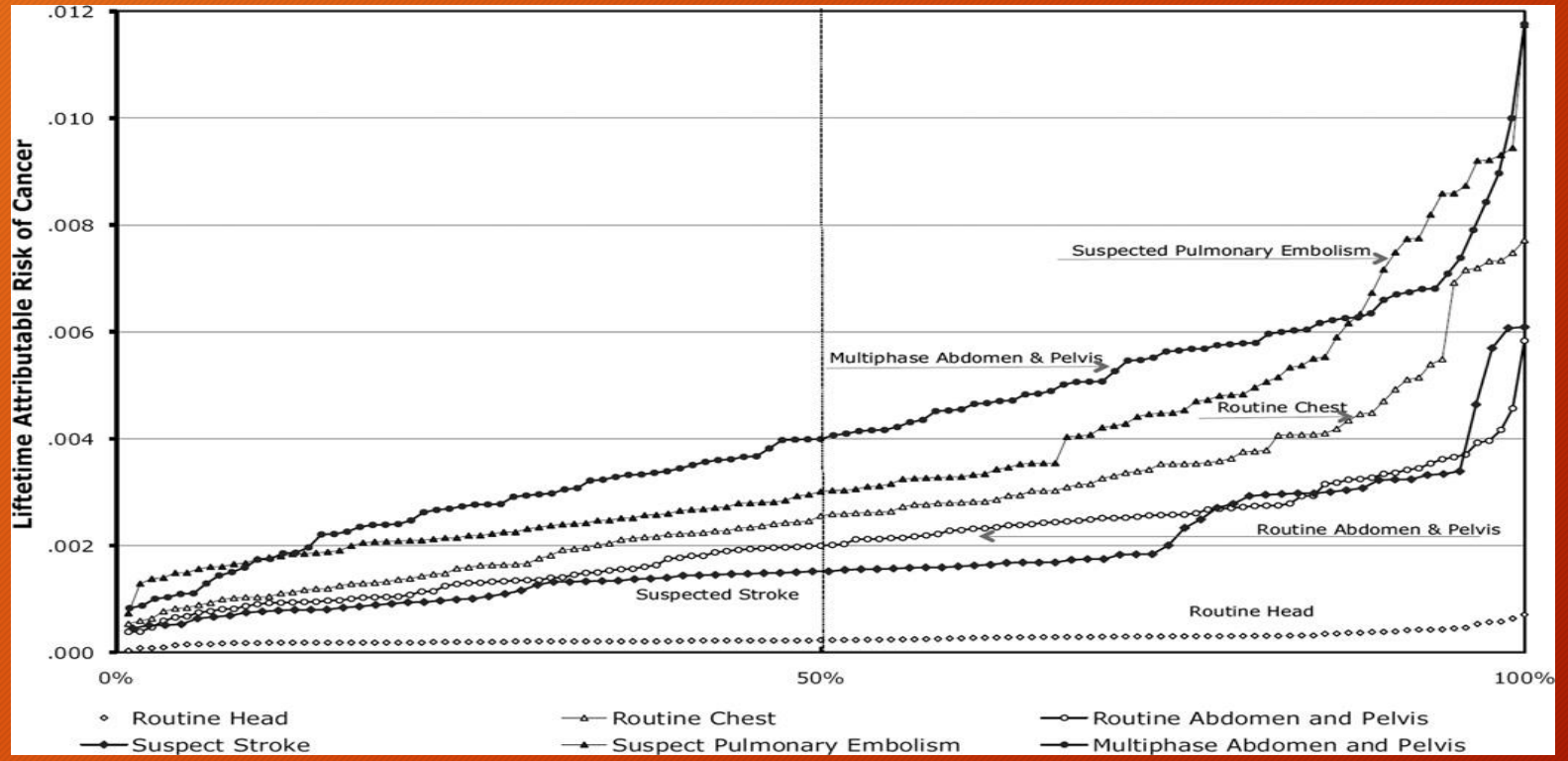
- Arch Intern Med. 2009 Dec 14; 169(22): 2078–2086.

Anatomic Area	Type of CT Study	CT Effective dose (mSv)			Conventional Radiographs Resulting in Equivalent Dose	
		Median	Interquartile Range	Absolute Range [Min, Max]	Chest X-ray Series	Mammography Series
Head and Neck	Routine Head	2.1	1.8 2.8	[0.27,5.8]	30	5
	Routine Neck	3.9	2.6 5.6	[0.72, 8.8]	55	9
	Suspected Stroke	14	9.4 20	[4.1, 56]	199	33
Chest	Routine Chest, no contrast	8.2	5.1 11	[1.7, 24]	117	20
	Routine Chest, with contrast	8.3	4.9 12	[1.6, 19]	119	20
	Suspected Pulmonary Embolism	9.6	7.0 14	[2.3, 30]	137	23
	Coronary Angiogram	22	14 24	[6.5, 39]	309	51
Abdomen - Pelvis	Routine Abdomen-Pelvis, no contrast	15	10 20	[2.9, 43]	220	37
	Routine Abdomen-Pelvis, with contrast	16	11 20	[4.0, 45]	234	39
	Multiphase Abdomen-Pelvis	31	21 43	[6.4, 90]	442	74
	Suspected Aneurysm or Dissection	24	20 37	[4.1, 68]	347	58

Variation in doses from CT scans



Adjusted Lifetime Attributable Cancer Risks



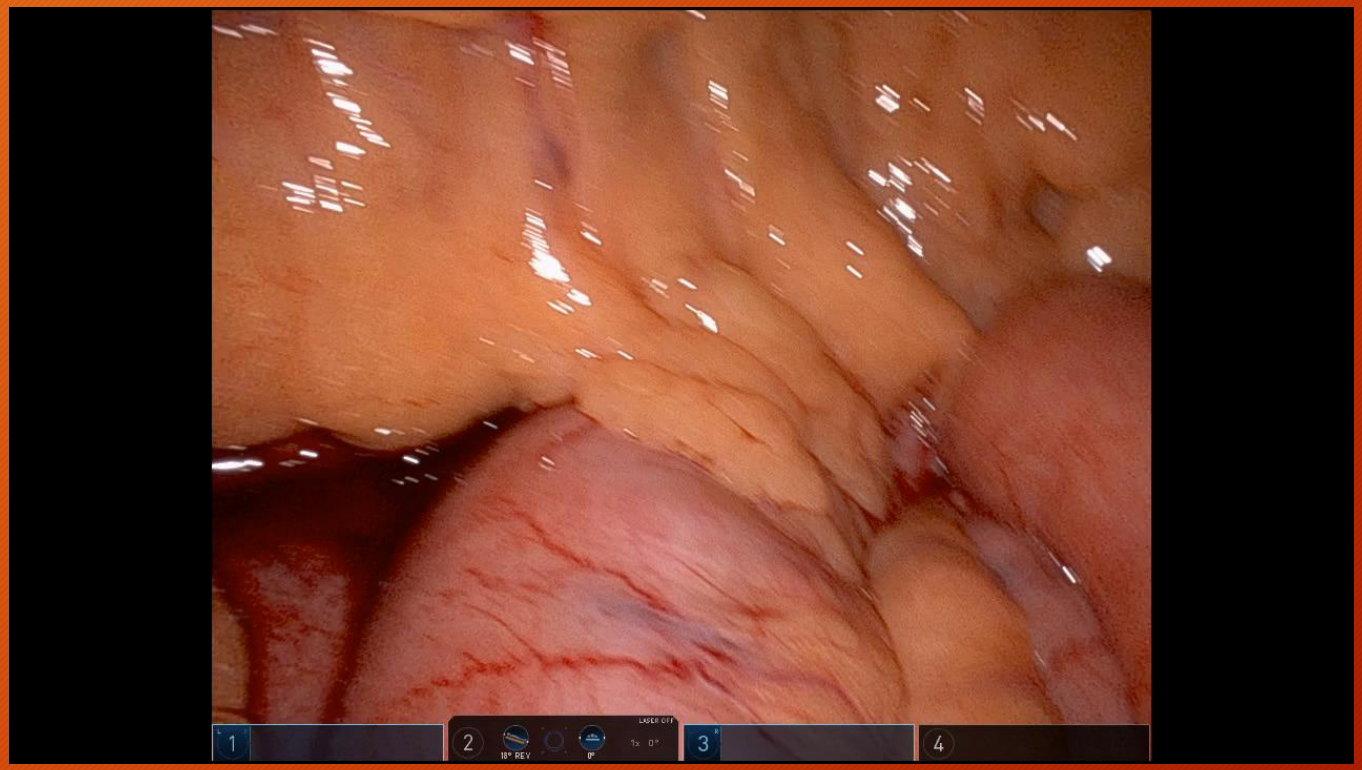
Anatomic Area	Type of CT Study	20 Year Old		40 Year Old		60 Year Old	
		Female	Male	Female	Male	Female	Male
		Median (25% 75%)	Median (25% 75%)	Median (25% 75%)	Median (25% 75%)	Median (25% 75%)	Median (25% 75%)
Head and Neck	Routine Head	4360 (3290, 5110)	7350 (5540, 8620)	8100 (6110, 9500)	11080 (8350, 12990)	12250 (9230, 14360)	14680 (11070, 14680)
	Routine Neck	2390 (1640, 3540)	4020 (2770, 5970)	4430 (3050, 6580)	6058 (4170, 8990)	6700 (4620, 9940)	8030 (5530, 8030)
	Suspected Stroke	660 (460, 980)	1120 (770, 1650)	1230 (850, 1820)	1682 (1170, 2490)	1860 (1290, 2750)	2230 (1550, 2230)
Chest	Routine Chest, no contrast	390 (290, 630)	1040 (770, 1670)	720 (540, 1160)	1566 (1170, 2520)	1090 (820, 1760)	2080 (1550, 2080)
	Routine Chest, with contrast	380 (270, 650)	1020 (710, 1740)	720 (500, 1210)	1538 (1070, 2620)	1070 (750, 1830)	2040 (1420, 2040)
	Suspected Pulmonary Embolism	330 (230, 460)	880 (610, 1220)	620 (420, 850)	1333 (920, 1840)	930 (640, 1280)	1770 (1220, 1770)
	Coronary Angiogram	150 (130, 230)	390 (350, 610)	270 (250, 420)	595 (540, 920)	420 (370, 640)	790 (710, 790)
Abdomen and Pelvis	Routine Abdomen-Pelvis, no contrast	500 (380, 770)	660 (510, 1024)	930 (710, 1430)	1002 (770, 1540)	1400 (1080, 2160)	1330 (1020, 1330)
	Routine Abdomen-Pelvis, with contrast	470 (380, 700)	620 (510, 930)	870 (710, 1300)	942 (770, 1400)	1320 (1080, 1960)	1250 (1020, 1250)
	Multiphase Abdomen-Pelvis	250 (180, 370)	330 (240, 490)	460 (330, 680)	498 (360, 730)	700 (500, 1030)	660 (480, 660)
	Suspected Aneurysm or Dissection	320 (210, 390)	420 (280, 510)	590 (390, 710)	636 (420, 770)	890 (580, 1080)	840 (550, 840)

Treatment Options

- Management of Localized Renal Cell Carcinoma
- 1. Radical Nephrectomy:

- Prototypical concept of early ligation of renal artery and vein with dissection external to Gerota's fascia, excision of ipsilateral adrenal gland, and performance of extended LND (crus of diaphragm to bifurcation of aorta)
- Select cases of adrenal sparing radical nephrectomy in absence of radiographic adrenal involvement and lower pole tumors
- Controversy regarding LND and depends on radiographic findings, age, tumor characteristics, and comorbidities

Surgical Video of Radical Nephrectomy



Treatment Options

- 2. Partial Nephrectomy:
- - preferred for tumors < 4 cm and location based
- - solitary kidney or conditions in which RN would render the patient anephric or at high risk of dialysis
- - for bilateral synchronous RCC must try to preserve as much renal tissue as possible
- - recurrence rates after RN 3-5%
- - number of preserved nephrons is the primary factor determining renal function after PN (ischemic injury plays a secondary role)
- Renal Hyperfiltration injury (proteinuria initial manifestation)

Thermal Ablative Therapies

- Radiofrequency ablation and cryoablation
- Indicated for advanced age and those with significant comorbidities
- Recurrence after partial nephrectomy
- Hereditary RCC with multifocal lesions
- Both can be done percutaneously or via laparoscopic approach
- Ideal tumor location is posterior and exophytic
- -20 degrees C ideal temp for cellular destruction (ice ball to extend 1 cm beyond margin of tumor)
- Follow up imaging paramount to determine recurrence
- Surgical treatment of post ablation recurrences extremely complicated due to extensive fibrosis (usually leads to nephrectomy)
- Complications include UPJ stricture, bleeding, ARF, pancreatitis, ileus, local organ injury, lumbar radiculopathy

Percutaneous Ablation vs Partial Nx

- *A Comparison of Percutaneous Ablation Therapy to Partial Nephrectomy for cT1a renal Cancers: results from the Canadian Kidney Cancer Information System*

  Millan et al

- 275 pts underwent AT and 2001 underwent PN
- 2 year median follow up
- RFS following AT and PN (88.1% and 97.4%, $p < 0.0001$)
- OS at 2 years for AT and PN (97.4% and 99%, $p = 0.7$)
- RFS at 5 years for AT and PN (86% and 95.1%, $p = 0.003$)
- OS at 5 years for AT and PN (94.2% and 95.1%, $p = 0.9$)

Active Surveillance

- Average growth rate of small renal masses 0.12-0.34 cm/year with low rate of metastasis
- Ideal for those patients that are poor surgical candidates, multiple comorbidities, or elderly
- Must image every 6-12 months for follow up

Active Surveillance for SRM

- Active Surveillance versus Immediate Intervention for Small Renal Masses: A Cost-Effectiveness and Clinical Decision Analysis

  Su et al

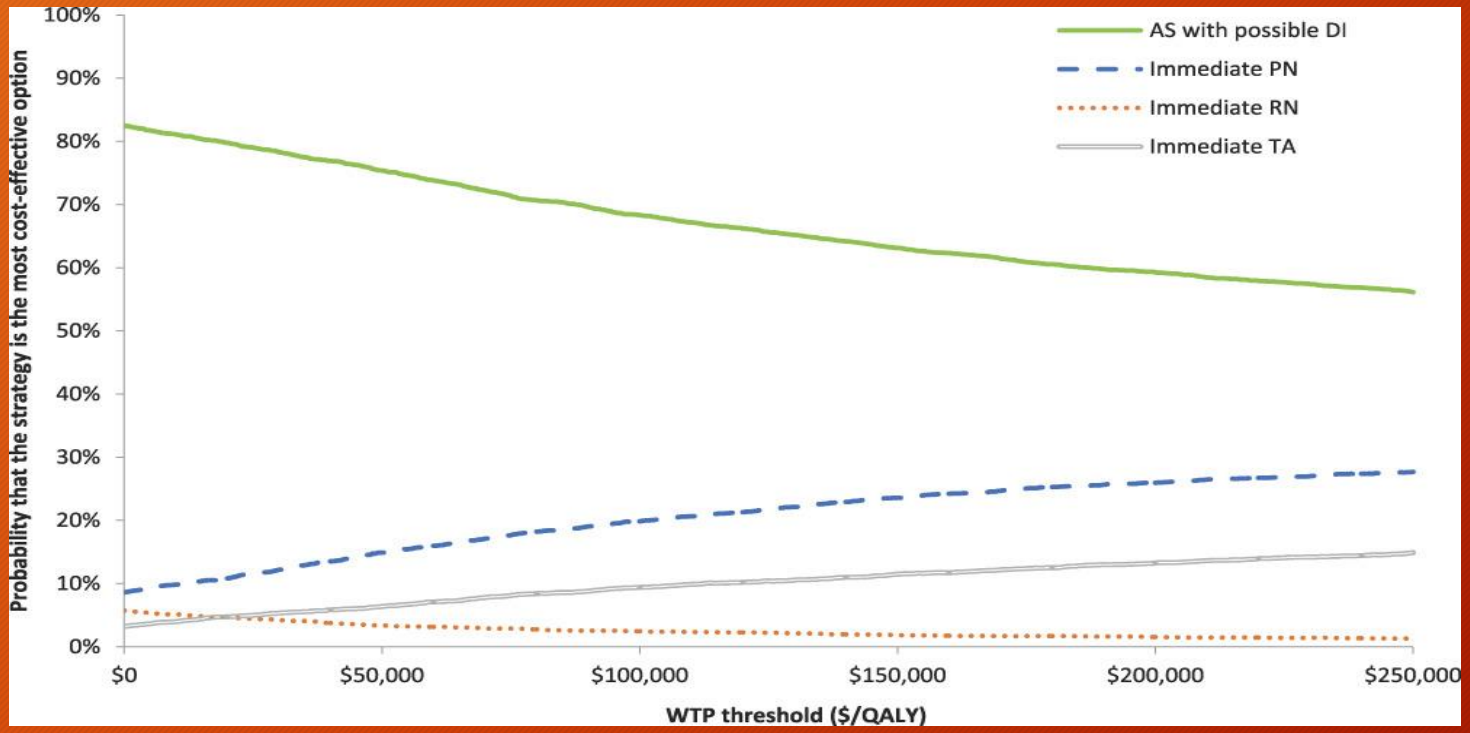
- Estimated the health outcomes and cost of 4 management strategies for 65-year-old patients with an incidental SRM
- AS with possible delayed intervention, immediate radical nephrectomy, immediate partial nephrectomy, and thermal ablation
- Evaluated mortality, direct medical costs, quality-adjusted life years, and incremental cost-effectiveness over 10 years

Active Surveillance for SRM

- Table . Base-case analysis results

10-Yr Model Outcome	Immediate PN	Immediate RN	Immediate TA	AS with Possible DI
Mortality rates (%):				
CKD-related mortality*	1.7	2.5	1.2	1.1
RCC-related mortality†	2.9	2.2	5.3	4.3
Operative mortality‡	0.1	0.6	0.04	0.1
Mortality due to other causes	17.3	17.2	17.1	17.2
All-cause mortality	21.9	22.4	23.7	22.6
Discounted per-patient totals:‖				
Total costs ($)	64,229	68,552	68,851	53,028
Total life-yrs	7.94	7.89	7.89	7.91
Total QALYs	6.23	6.12	6.23	6.18
Cost-effectiveness analysis results (vs AS with possible DI):				
Δ Total costs ($)	11,201	15,524	15,823	-
Δ Total life-years	0.03	−0.02	−0.02	-
Δ Total QALYs	0.05	−0.06	0.05	-
ICER ($/QALY)¶	206,181	Dominated	335,488	

AS for SRM

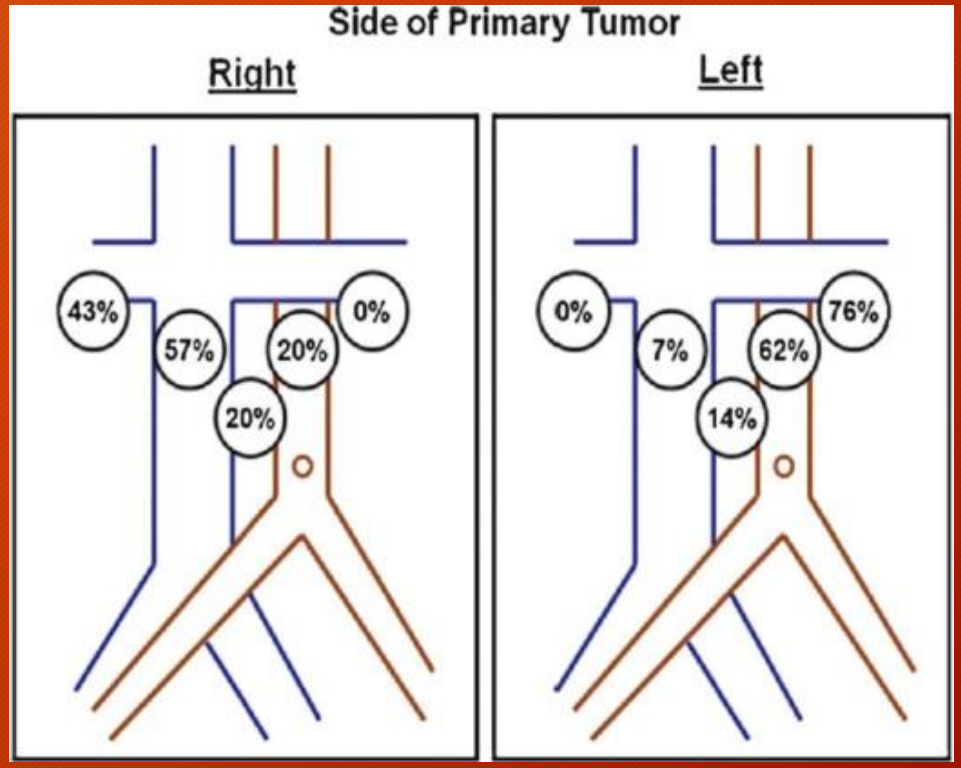

Probability that the strategy is the most cost-effective option
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
$0
$50,000
$100,000
$150,000
$200,000
$250,000
WTP threshold ($/QALY)
AS with possible DI
Immediate PN
Immediate RN
Immediate TA

Active Surveillance for SRM

- AS was the most effective strategy if the annual probability of metastatic progression from AS was sufficiently low: this threshold was 0.35%–0.45% for ages <81 years at baseline and at least 0.20% for ages 81–85 years
- Decision analytic modeling suggests that AS with timely DI has a comparable 10-year all-cause mortality and is cost-effective for managing patients with incidental SRMs in comparison to immediate PN, RN, and TA
- Conditions in which immediate intervention for SRMs is preferred over AS are quantitatively characterized: the metastatic potential of SRMs needs to be sufficiently high in relation to patient age for immediate intervention to be preferred.
- Conditions that favor immediate PN include low patient age, poor tolerance of AS, good health status, and a low risk of renal function loss after surgery.
- Conditions favoring immediate TA include advanced age and poor health status.
- A main benefit of AS is avoiding the morbidity and mortality of CKD development after interventions on benign or indolent tumors, but this must be evaluated against the potential risk of metastatic progression on AS

Lymph Node Dissection for RCC

- Increasing number of risk factor=increased risk of LN mets
- Patients with 2 or more risk factors should undergo extensive LN dissection
- Risk factors include: Fuhrman grade 3 or 4, sarcomatoid component, tumor size >10 cm, pT3 or pT4, histological necrosis



Local Recurrence after RN/PN

- Occurs in renal fossa, ipsilateral adrenal gland, or ipsilateral retroperitoneal LNs
- 2-4% of cases
- Risk factors include: locally advanced or node-positive disease, and adverse histopathologic features
- Only about 40% of local recurrences are isolated
- Majority of those with local recurrence also have systemic disease
- If neighboring organs involved- en bloc resection (tissue planes disrupted and tissue barriers are no longer present)
- Recurrence after PN anywhere from 1.4-10%
- Most are distant from the tumor bed due to unrecognized tumor multicentricity or de novo occurrence
- Can treat those isolated recurrences after PN with AS, PN, completion nephrectomy, or TA

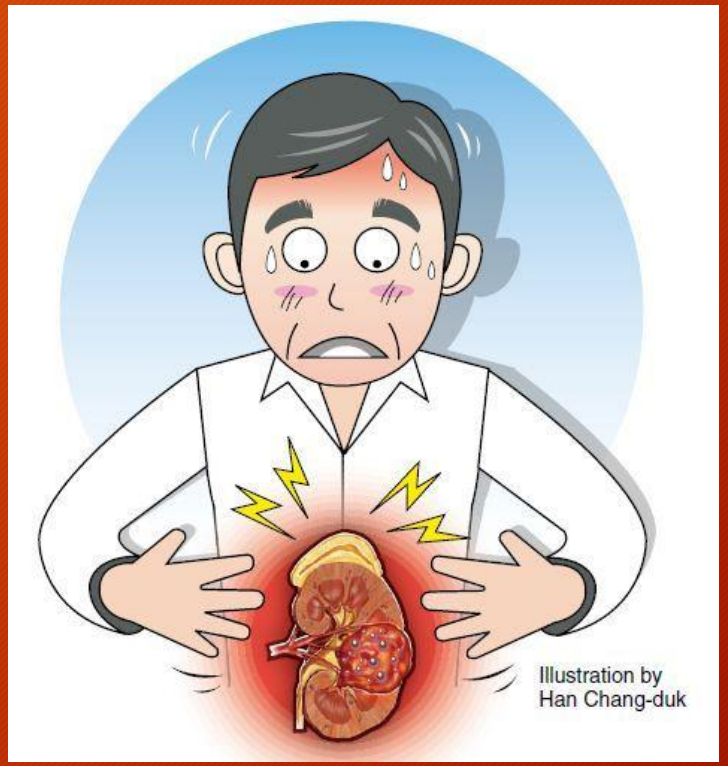


Illustration by
Han Chang-duk

Adjuvant Treatments for RCC

- 1. Tyrosine Kinase inhibitors: VEGF inhibitor (anti-angiogenesis)
- Sunitinib
- Sorafenib
- Pazopanib
- Cabozantinib
- Bevacizumab
- Axitinib

- Side effects include: nausea, rash, diarrhea, hand-foot-syndrome, CHF, mouth sores, weakness, neutropenia, hypothyroidism, fatigue, HTN

Adjuvant Treatments for RCC

- 2. mTOR inhibitors: blocks protein for cell growth
- Temsirolimus
- Everolimus

- Side effects include: nausea, fatigue, rash, loss of appetite, mouth sores, weakness, edema, increases in blood sugar and cholesterol

Adjuvant Treatments for RCC

- 3. PD-1 Inhibitors:
- - immune checkpoint inhibitors targeting protein (PD-1) on T cells which normally prevent attack on other cells in body
- Pembrolizumab
- Nivolumab
- Side effects include: fatigue, cough, rash, loss of appetite, nausea, itching, joint pain, constipation, diarrhea

- 4. Cytokines:
- Interleukin-2 and Interferon alpha
- IL-2 given in hospital setting due to potential for serious side effects
- Capillary leak syndrome, neutropenia, thrombocytopenia, leukopenia, flu-like symptoms, rash, diarrhea, liver and renal failure, mouth ulcers, hypothyroidism

Adjuvant Treatment for RCC

- ASSURE trial- sunitinib vs sorafenib vs placebo
- EVEREST trial- everolimus vs placebo
- PROTECT trial- pazopanib vs placebo

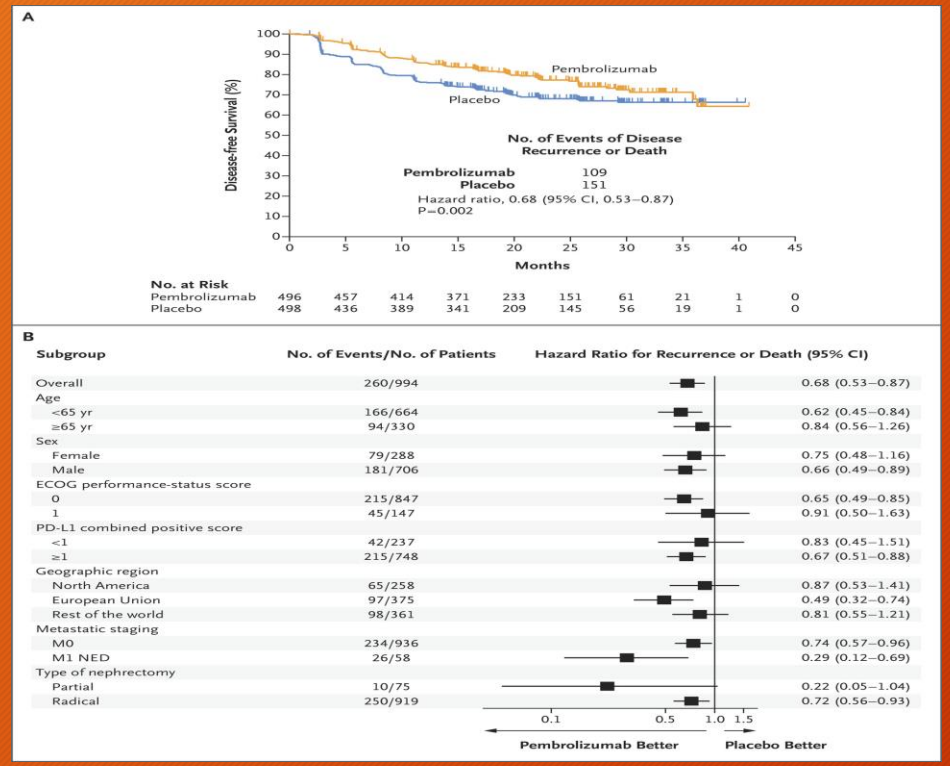
Adjuvant Treatment for RCC

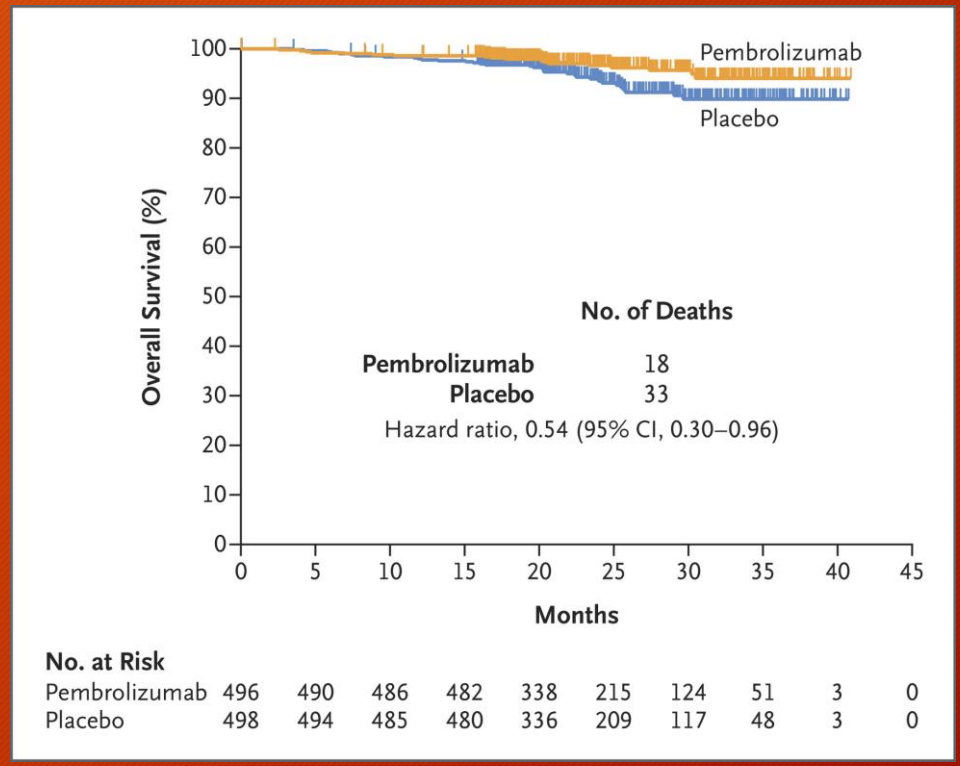
- Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma
- August 19, 2021
  N Engl J Med 2021; 385:683-694
- Double-blind, phase 3 trial, randomly assigned, in a 1:1 ratio, patients with clear-cell renal-cell carcinoma who were at high risk for recurrence after nephrectomy, with or without metastasectomy, to receive either adjuvant pembrolizumab (at a dose of 200 mg) or placebo intravenously once every 3 weeks for up to 17 cycles (approximately 1 year)
- The primary end point was disease-free survival
- Overall survival was a key secondary end point
- Safety was a secondary end point

Adjuvant Treatment for RCC

- 496 patients to receive pembrolizumab and 498 patients in placebo group
- median time from randomization to the data-cutoff date was 24.1 months
- Pembrolizumab therapy was associated with significantly longer disease-free survival than placebo (disease-free survival at 24 months, 77.3% vs. 68.1%; hazard ratio for recurrence or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P=0.002)
- percentage of patients who remained alive at 24 months was 96.6% in the pembrolizumab group and 93.5% in the placebo group (hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96)
- Grade 3 or higher adverse events of any cause occurred in 32.4% of the patients who received pembrolizumab and in 17.7% of those who received placebo
- The risk of disease recurrence or death was 32% lower with adjuvant pembrolizumab therapy than with placebo

Adjuvant Treatment for RCC





Adjuvant Treatment for RCC

Table 2. Any-Cause and Treatment-Related Adverse Events (As-Treated Population).*

Event	Pembrolizumab (N=488)	Placebo (N=496)
	no. of patients with event (%)	
Any-cause adverse events		
Adverse event of any grade	470 (96.3)	452 (91.1)
Adverse event of grade 3 to 5	158 (32.4)	88 (17.7)
Discontinuation of pembrolizumab or placebo due to adverse event	101 (20.7)	10 (2.0)
Death due to adverse event	2 (0.4)	1 (0.2)
Serious adverse event	100 (20.5)	56 (11.3)
Discontinuation of pembrolizumab or placebo due to serious adverse event	49 (10.0)	5 (1.0)
Treatment-related adverse events, as assessed by investigator		
Adverse event of any grade	386 (79.1)	265 (53.4)
Adverse event of grade 3 to 5	92 (18.9)	6 (1.2)
Discontinuation of pembrolizumab or placebo due to adverse event	86 (17.6)	3 (0.6)
Death due to adverse event	0	0
Serious adverse event	59 (12.1)	1 (0.2)
Discontinuation of pembrolizumab or placebo due to serious adverse event	37 (7.6)	0

* The as-treated population included all the patients who received at least one dose of pembrolizumab or placebo. Adverse events were recorded from randomization through 30 days after the discontinuation of pembrolizumab or placebo. Serious adverse events were defined as any adverse event that resulted in death, was life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was judged by the investigator to be a serious adverse event. Serious adverse events were recorded from randomization through 90 days after the discontinuation of pembrolizumab or placebo.

Adjuvant Treatment for RCC

Table 3. Any-Cause Adverse Events with an Incidence of at Least 10% in Either Group (As-Treated Population).*

Event	Pembrolizumab (N=488)		Placebo (N=496)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
Fatigue	145 (29.7)	5 (1.0)	120 (24.2)	0
Diarrhea	124 (25.4)	8 (1.6)	111 (22.4)	1 (0.2)
Pruritus	111 (22.7)	1 (0.2)	65 (13.1)	0
Arthralgia	108 (22.1)	2 (0.4)	93 (18.8)	2 (0.4)
Hypothyroidism	103 (21.1)	1 (0.2)	18 (3.6)	0
Rash	98 (20.1)	4 (0.8)	53 (10.7)	2 (0.4)
Nausea	80 (16.4)	2 (0.4)	48 (9.7)	0
Cough	76 (15.6)	0	50 (10.1)	0
Headache	69 (14.1)	0	62 (12.5)	0
Hyperthyroidism	58 (11.9)	1 (0.2)	1 (0.2)	0
Asthenia	50 (10.2)	1 (0.2)	36 (7.3)	1 (0.2)
Increase in blood creatinine level	50 (10.2)	1 (0.2)	42 (8.5)	0
Back pain	49 (10.0)	1 (0.2)	64 (12.9)	1 (0.2)

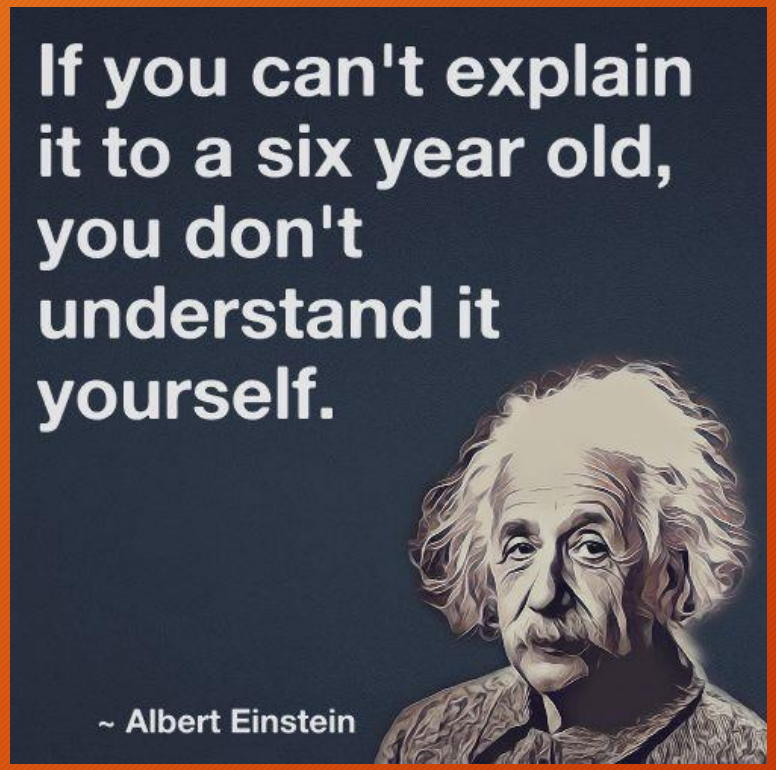
* No adverse events of grade 4 or 5 occurred in at least 10% of the patients in either group.

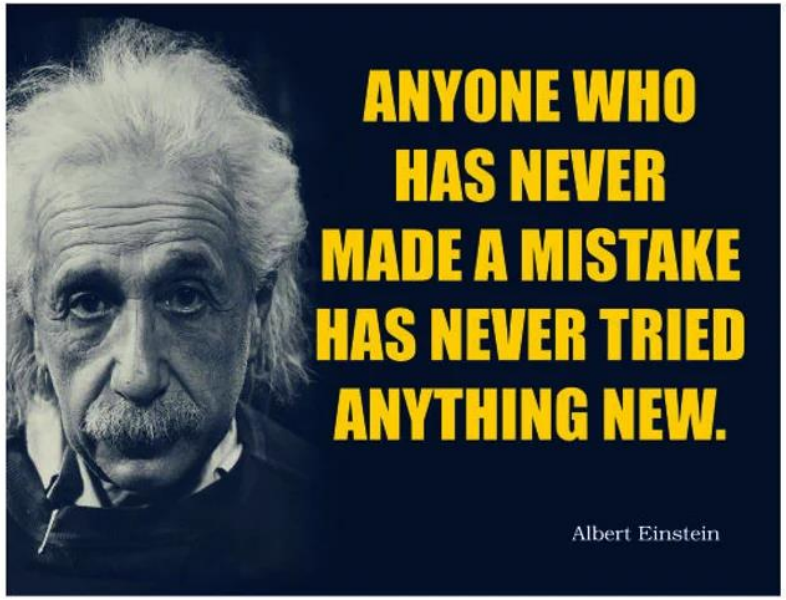
Conclusion

- RCC is most commonly found on imaging for non-Urological symptoms
- If found early, RCC is a very treatable with SURGERY!
- Utilization of Active Surveillance in specific populations
- Early referral to the Urologist paramount!!
- Advanced RCC can be lethal so collaboration with medical oncology critical
- Avoid excess radiation exposure by utilizing MRI or Ultrasound
- STOP: CT scanning in pediatric population (think **Ultrasound!**)

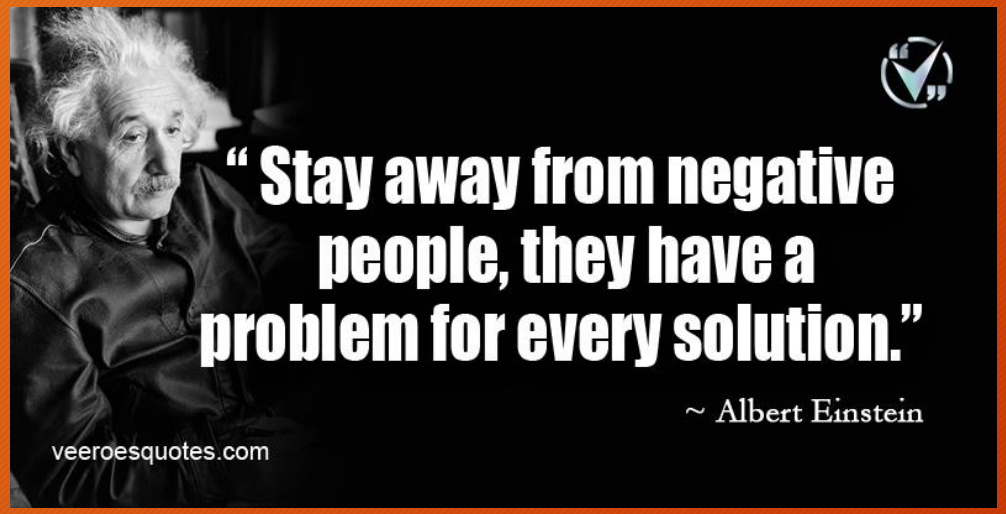
WE CAN CONQUER THIS!!

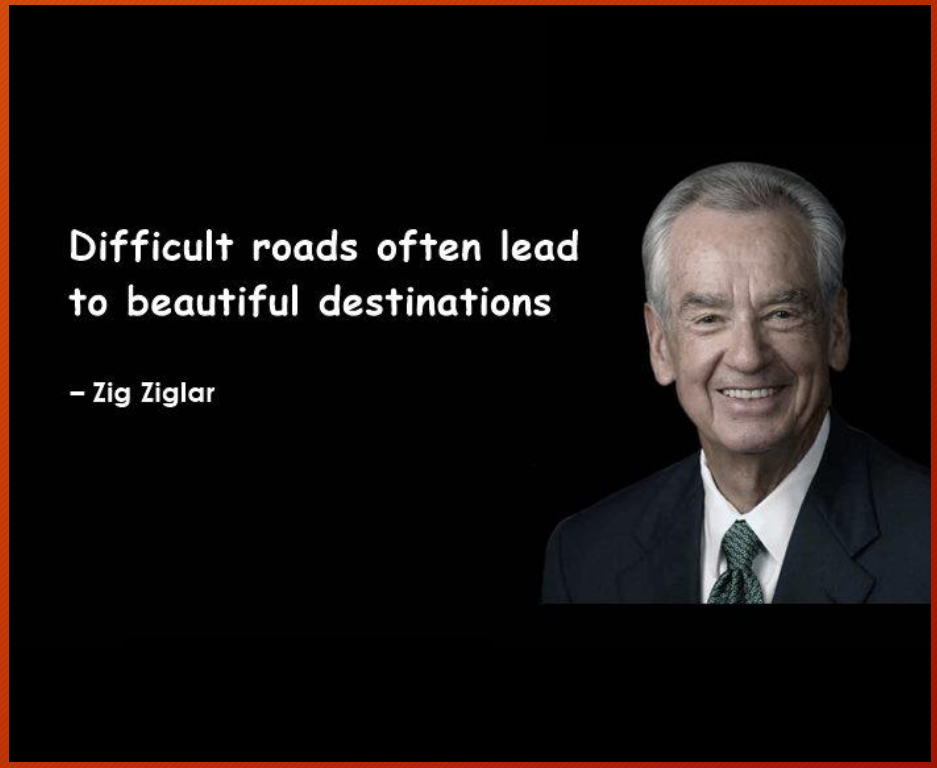
Inspiration!





Inspiration!





Thank You!