Disease and patient characteristics for adjuvant kidney cancer trials

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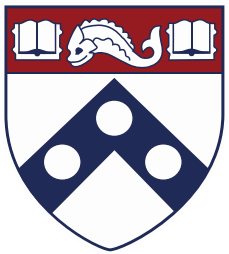
November 28, 2017



Penn
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What are the most important drivers of disease recurrence?

- Histology?
- Molecular pathways?
- Grade?
- Stage?
- Immune or other health of the patient?

Discrepancies between some industry and cooperative adjuvant trials

	Central radiology review	How likely are independent reviews to differ from those of the treating MD?
	Central pathology review	Essential if we are going to understand differences in tumor characteristics
	Stage inclusion	All likely to be offered therapy in the future or only very high risk?
	Histology inclusion	ccRCC or all histologies?
	Frequency of scan/other monitoring	NCCN driven or more frequent, based on financial support
	Statistical analyses	
	Criteria for censoring	Early dropout- recurrence or toxicity?
	Management of dosing Management of toxicity	Variability in doses allowed How we count days not treated

Consensus for adjuvant trials
5 big issues

- Histology
- Patient populations
- Endpoints
- Use of placebo controls/ unblinding
- Biomarkers?
- Imaging baseline and at recurrence
- Statistical variabilities

Consensus for adjuvant trials
5 big issues

- Histology and other tumor characteristics
  - Clear vs non-clear cell
  - Stage, grade, size
- Patient populations
  - Exclusion criteria
  - Performance status
  - susceptibility to toxicity?
- Use of placebo controls/ unblinding
- Biomarkers?
  - Potential role for biomarker driven trials
- Endpoints

Histology Challenges

- Histology vs molecular characteristics
- Impact of TCGA
- Heterogeneity

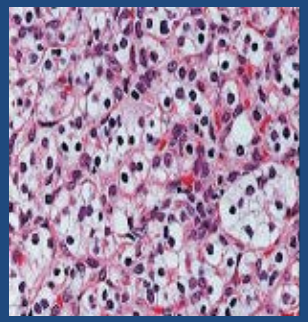
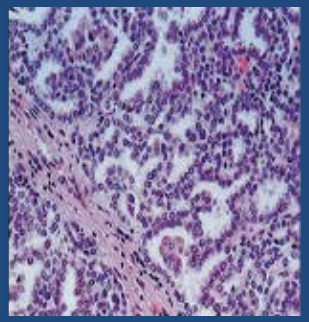
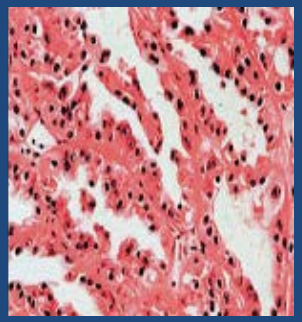
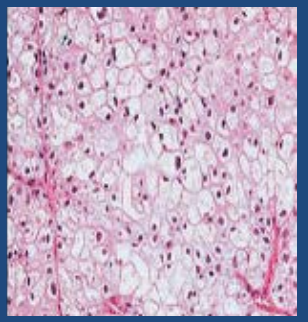
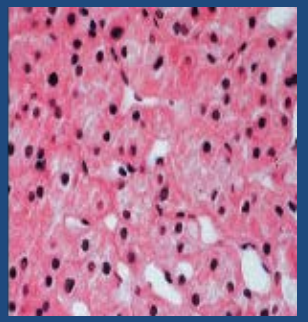
Clear vs non-clear…what is clear cell?

Defining by histology is the current practice

***2004 WHO lists over 50 different types of kidney cancer**

(Sarcomatoid variant can occur with any subtype)

Undifferentiated type and Collecting duct carcinoma constitute the other 2 types listed in AJCC classification

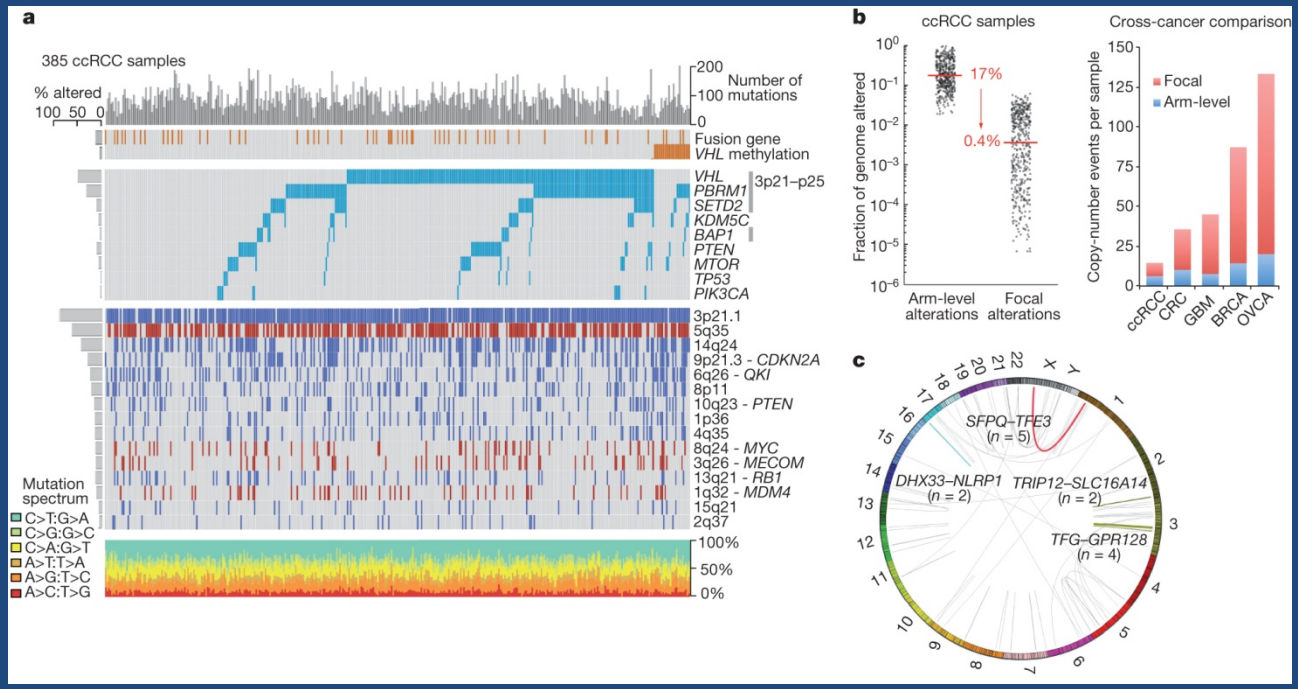






Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Incidence (%)	*75%*	*5%*	*10%*	*5%*	*5%*
Associated mutations	*VHL*	*c-Met*	*FH*	*BHD*	*BHD*

BHD=Birt-Hogg-Dubé; FH=fumarate hydratase; VHL=von Hippel-Lindau.

Modified from Linehan WM et al. *J Urol*. 2003;170:2163-2172.

Somatic alterations in ccRCC
Many signatures for clear cell RCC.

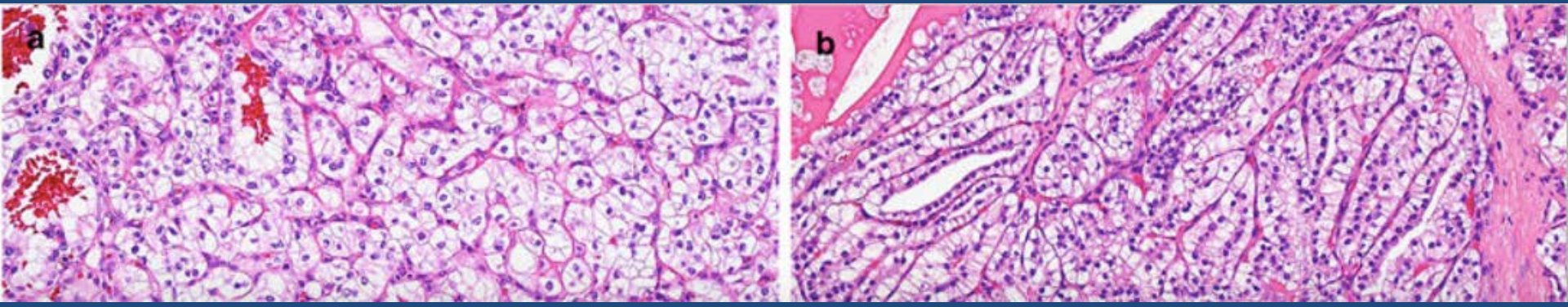


CJ Creighton *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12222

nature

One example: clear cell might not be “clear cell”

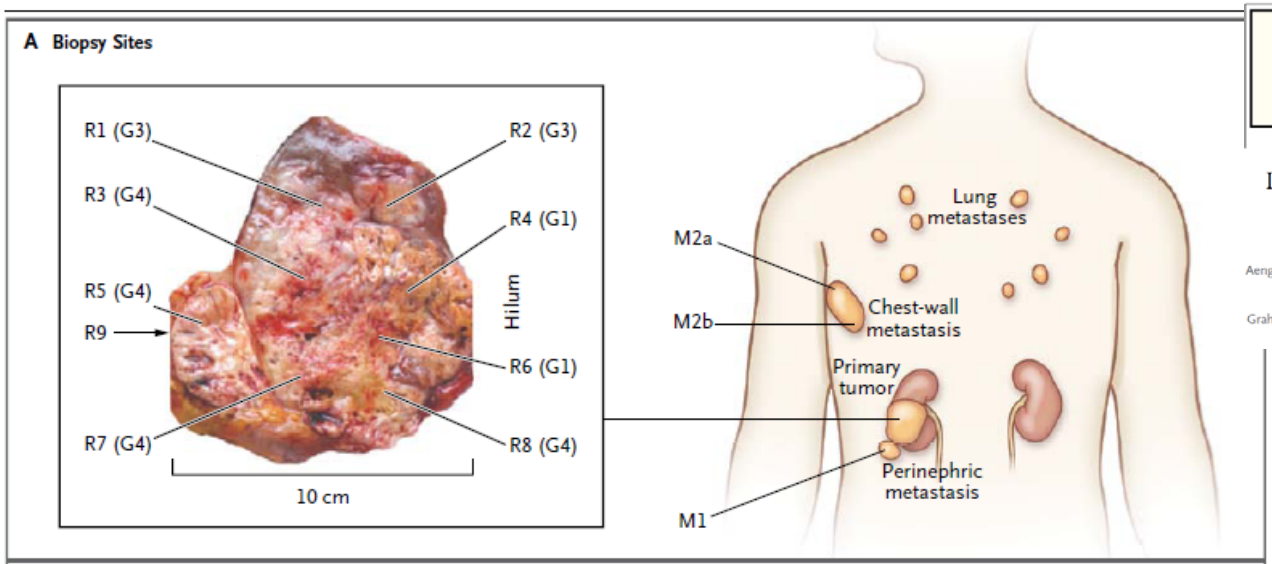
- Clear cell papillary renal cell carcinoma
- Lower grade, confused with clear cell RCC
- Lacks VHL mutations and 3p deletions
- exhibit co-expression of CK7 and CAIX at the immunohistochemical level, coupled with negative reactions for AMACR.
- Gobbo S, Eble JN, Grignon DJ *et al* Clear cell papillary renal cell carcinoma: a distinct histopathologic and molecular genetic entity. *Am J Surg Pathol* 2008;**32**:1239–1245.

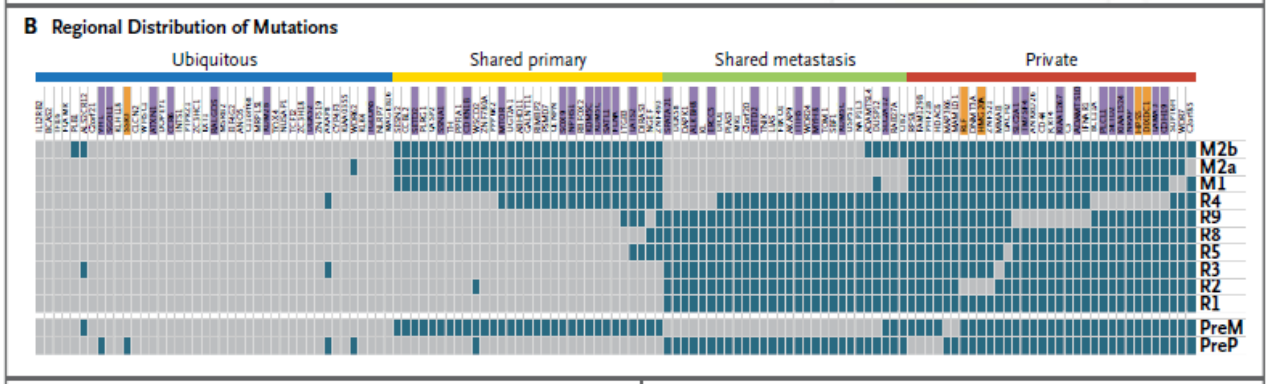


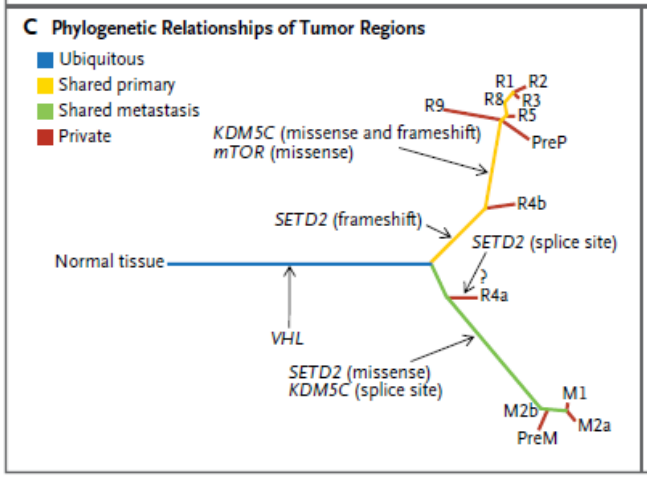
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

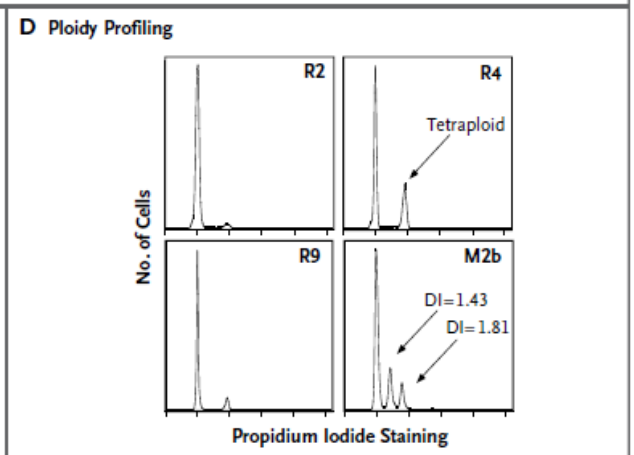
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.









Heterogeneity confounds interpretation when limited slides are available for review

A word on Grade/T stage

- New AJCC recommendations
- Nuclear grade, not Fuhrman grade
- Satish Tickoo“if you see pT2, keep looking…probably pT3 (no longer require muscle in vessel walls to call tumor seen in vessels as vascular invasion)”
- Thus, pathologists, clinicians and scientists must work together to keep each other up to date

Patient populations: Which shall we include/exclude?

- Depends on the agent to be tested
  - Patients with poor organ function?
  - Patients with autoimmune diseases (if immune checkpoint agents)
  - Patients with non aggressive malignancies unlikely to affect outcome
- Depends on the goals of the clinical trial
  - “cleaner eligibility criteria” less of a chance of confounding interpretation of toxicity
  - Real world patients- those treated after agents are commercially approved

Endpoints:
Goals of adjuvant therapy

- Cure disease that would otherwise result in metastases and death (Overall survival as endpoint)
- Control disease that would otherwise result in metastases (Disease free survival as endpoint)

Placebo controls

- Pros
  - Can help prevent MD and patients from treatment deviations
- Cons
  - decrease study participation
  - Patients don't like placebo controls..suspicion, etc
  - Study monitors reluctant to unblind patients at recurrence

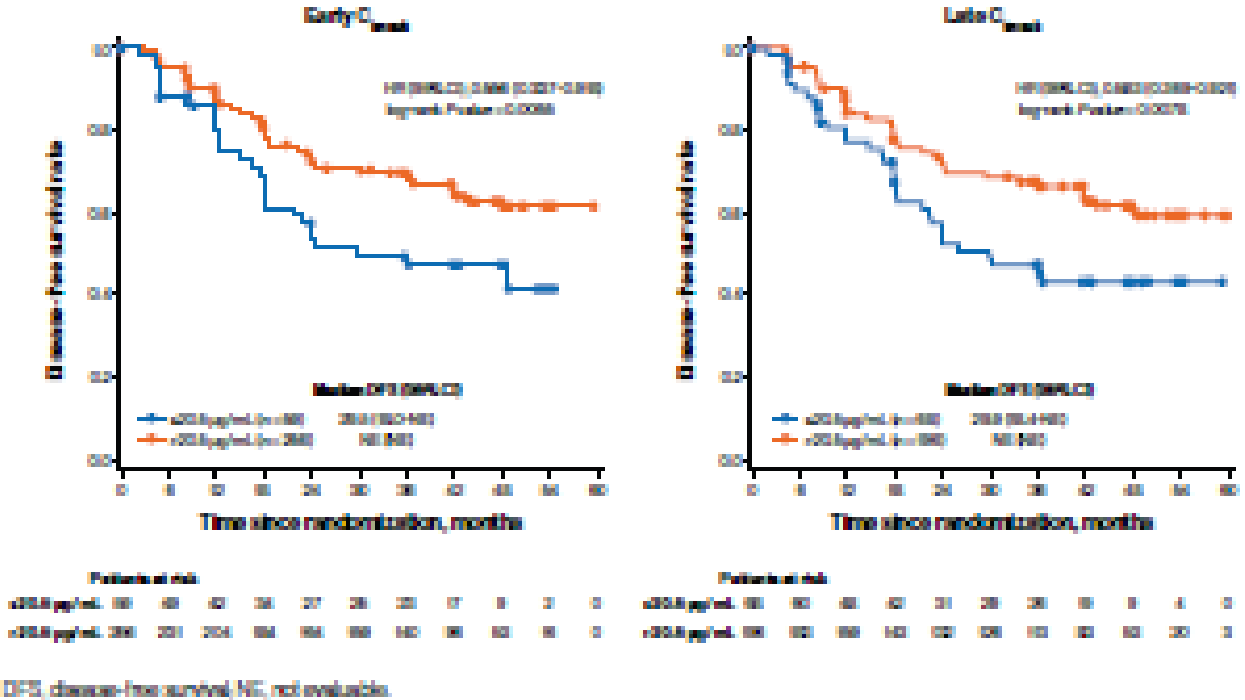
Ability to use biomarkers, other tools to define eligibility

- Molecular/immune signatures?
- Toxicity profiles (c trough, pharmacokinetics now more apparent in VEGF TKI therapies)

Pharmacokinetics…could these be used?

PROTECT (ASCO 2017) Higher C trough associated with longer DFS but did not correlate with dose in the 600mg patient population

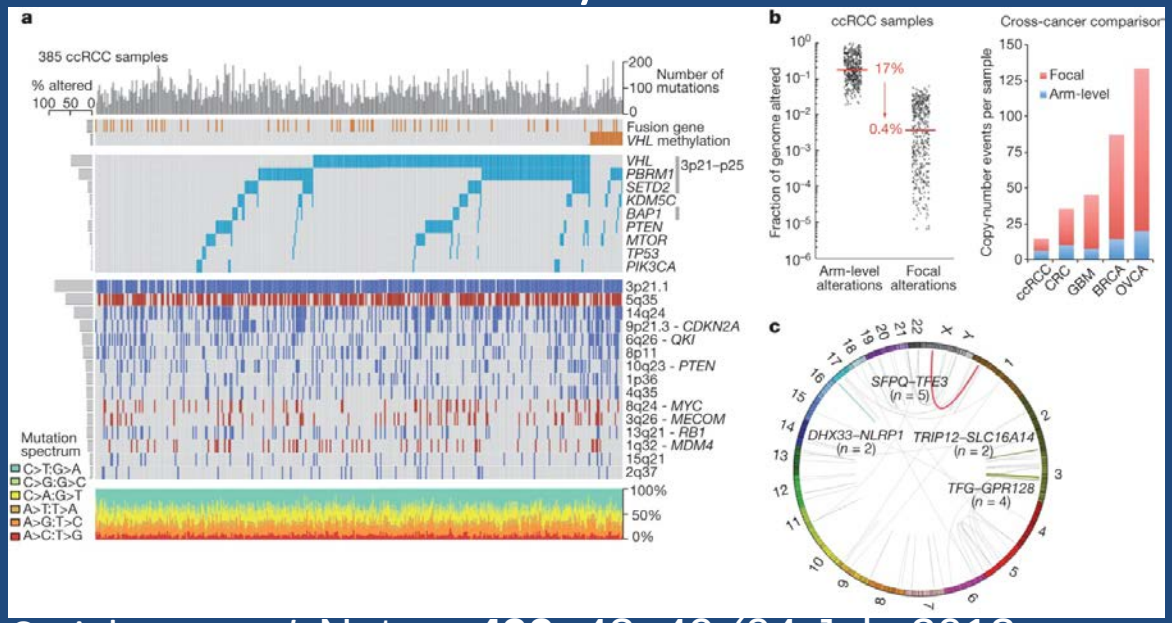
Figure 3. DFS by C_{trough} >20.6 µg/mL or ≤20.6 µg/mL.



DFS, disease-free survival; NE, not evaluable.

E2805 Clinical Trial Sequencing Project

- 600 clear cell RCC patients- 200 per arm (sunitinib, sorafenib, placebo)
- DNA sequencing (whole exome)
- RNA sequencing
- Bioinformatic analysis



CJ Creighton *et al.* Nature **499**, 43–49 (04 July 2013

S-TRAC

- Retrospective validation of oncotype Dx

Panel 1: Final recurrence score genes and gene g

Vascular
- *APOLD1*
- *EDNRB*
- *NOS3*
- *PPAP2B*

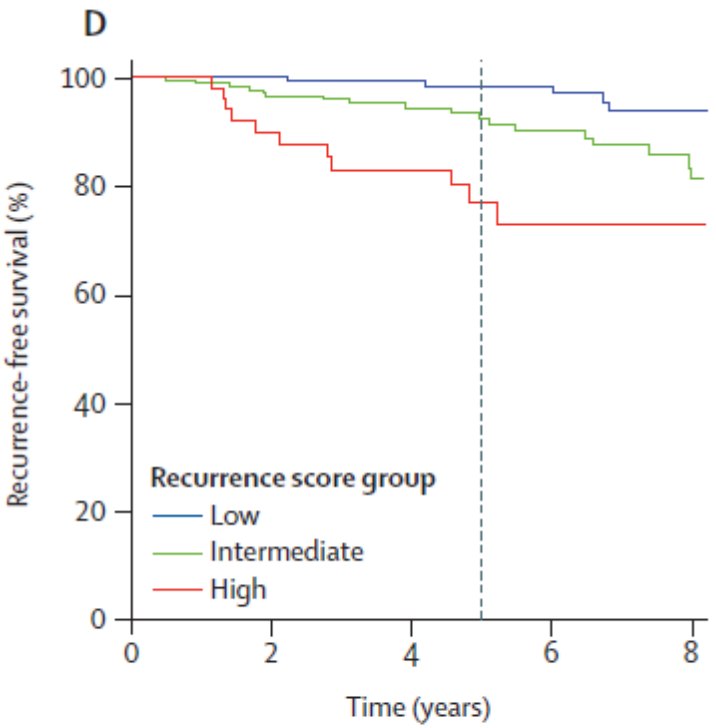
Cell growth/division
- *EIF4EBP1*
- *TUBB2A*
- *LMNB1*

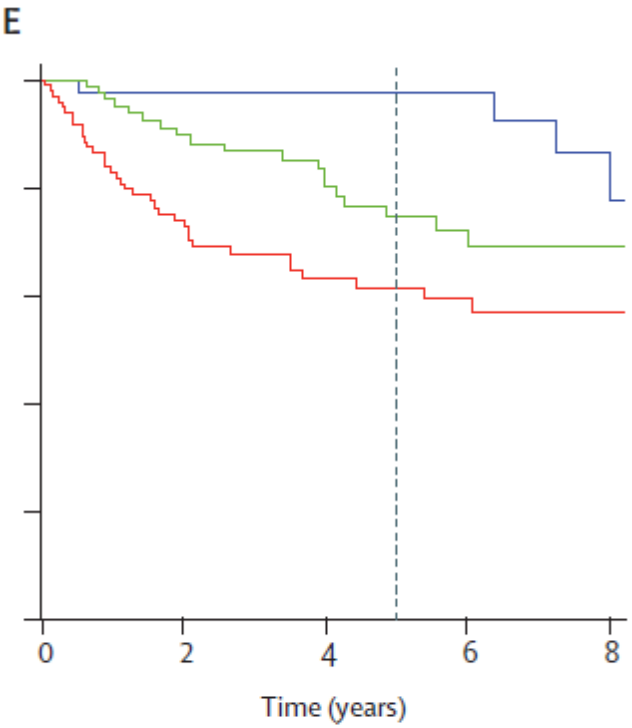
Immune response
- *CEACAM1*
- *CX3CL1*
- *CCL5*

Inflammation
- *IL6*

Reference
- *AAMP*
- *ARF1*
- *ATP5E*
- *GPX1*
- *RPLP1*

The recurrence score is based on 16 genes (11 cancer-related and five re
and is derived from the reference-normalised expression measurement
from 0 to 100.





Recurrence score group	N (%)	5-year risk (95% CI)
Low	156 (39%)	0·016 (0·004–0·065)
Intermediate	184 (46%)	0·076 (0·042–0·135)
High	58 (15%)	0·231 (0·129–0·392)

N (%)	5-year risk (95% CI)
43 (19%)	0·024 (0·003–0·161)
82 (37%)	0·255 (0·165–0·382)
99 (44%)	0·385 (0·289–0·500)

Rini B, et. al. Lancet Oncol. 2015 Jun;**16**(6):676-85.

EZH2 expression

VOLUME 35 · NUMBER 32 · NOVEMBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Validation of Enhancer of Zeste Homolog 2 Expression as an Independent Prognostic Marker in Localized Clear Cell Renal Cell Carcinoma

Thai Huu Ho, Payal Kapur, Jeanette E. Eckel-Passow, Alana Christie, Richard W. Joseph, Daniel J. Serie, John C. Cheville, R. Houston Thompson, Farrah Homayoun, Vandana Panwar, James Brugarolas, and Alexander S. Parker

Published OnlineFirst January 19, 2015; DOI: 10.1158/0008-5472.CAN-14-2931

Molecular and Cellular Pathobiology

Cancer Research

Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205

Hiroshi Hirata[1], Yuji Hinoda[2], Varahram Shahryari[1], Guoren Deng[1], Koichi Nakajima[3], Z. Laura Tabatabai[4], Nobuhisa Ishii[3], and Rajvir Dahiya[1]

Things that can affect outcome

- Patient heterogeneity
  - Histology
  - Grade
  - Performance status/co-morbidities
  - Stage
  - Community vs academic vs country site
- Management of toxicity
  - Dose interruption, lowering of dose, who comes off study
- Definition of recurrence
  - Definition of radiographic recurrence
  - Frequency of scan intervals in follow-up
- Statistical adjustments
  - Feasibility
  - Increasing sample size

Conclusions

- Histology-
  - Include both clear and non clear cell disease if the study agent has activity in both
  - If exploratory in non-clear cell, then power to clear cell
  - consider wide spread wit statistics to address subgoups
- Patient populations
  - more lenient parameters can increase accrual without affecting outcome
  - Allow non active malignancies that are unlikely to affect outcome
  - Agent specific- allow patients with conditions unlikely to affect outcome
- Endpoints-DFS is useful but OS will convince MDs of clear role
  - Consider dual primary outcomes
- Use of placebo controls/ unblinding- must be transparent with the patients-
  - must unblind at recurrence
- Biomarkers?
  - EZH2
  - Others promising

Consensus for adjuvant trials
5 big issues

- Histology
- Patient populations
- Endpoints
- Use of placebo controls/ unblinding
- Biomarkers?

Baseline imaging

CT/MRI, not PET

Is IV contrast essential to identify baseline disease?

Patients and clinicians concerned about nephrotoxicity

If our therapies are effective enough should “a little bit of leftover disease” affect outcome

Should we include these patients?

Insights Imaging (2015) 6:553–558
DOI 10.1007/s13244-015-0420-2

REVIEW

Revisiting the risks of MRI with Gadolinium based contrast agents—review of literature and guidelines

Aurang Z. Khawaja[1] · Deirdre B. Cassidy[2] · Julien Al Shakarchi[1] · Damian G. McGrogan[1] · Nicholas G. Inston[1] · Robert G. Jones[3]

- certain gadolinium agents (Class 2) usually macrocyclic agents, are associated with few if any unconfounded cases of NSF
- Thus, use of contrast should not be of concern in most cases, including patients with reduced GFR

World J Radiol. 2013 Nov 28; 5(11): 436–445.
Published online 2013 Nov 28. doi: 10.4329/wjr.v5.i11.436
PMCID: PMC3856336

MDCT imaging following nephrectomy for renal cell carcinoma: Protocol optimization and patterns of tumor recurrence

Stephanie F Coquia, Pamela T Johnson, Sameer Ahmed, and Elliot K Fishman

World Journal of Radiology

PMC full text: World J Radiol. 2013 Nov 28; 5(11): 436–445.
Published online 2013 Nov 28. doi: 10.4329/wjr.v5.i11.436

Table 2

Most common locations of recurrence and their incidence after nephrectomy

Location	Incidence of Recurrence after Nephrectomy
Lung	38%-71%[3]
Lymph nodes	12%-63% (total within chest, abdomen, and pelvis)[3]
Liver	7%-23%[2]
Nephrectomy site	10%[2,8]
Contralateral kidney	1.2%-10%[3,9]
Adrenal gland	7%-10%[3]
Bone	18%-37%[3]
Brain	2%-15%[3,4]

FOLLOW-UP[a,b]
(category 2B)

Stage II or III

Follow-up After a Radical Nephrectomy

- **H & P every 3-6 mo for 3 y, then annually up to 5 y after radical nephrectomy and then as clinically indicated thereafter**
- **Comprehensive metabolic panel and other tests as indicated every 6 mo for 2 y, then annually up to 5 y after radical nephrectomy, then as clinically indicated thereafter**
- **Abdominal imaging:**
  - **Baseline abdominal CT or MRI within 3-6 mo, then CT, MRI or US (US is category 2B for Stage III), every 3-6 mo for at least 3 y and then annually up to 5 y**
  - **Imaging beyond 5 y: as clinically indicated**
  - **Site specific imaging: as symptoms warrant**
- **Chest imaging:**
  - **Baseline chest CT within 3-6 mo after radical nephrectomy with continued imaging (CT or chest x-ray) every 3-6 mo for at least 3 y and then annually up to 5 y**
  - **Imaging beyond 5 y: as clinically indicated based on individual patient characteristics and tumor risk factors**
- **Pelvic imaging, as clinically indicated**
- **CT or MRI of head or MRI of spine, as clinically indicated**
- **Bone scan, as clinically indicated**

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