Surgical Considerations (Impediments) for Adjuvant Therapy Trials:

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We are all managers of health care risk

We seek to understand, predict and prevent future health care events

Adjuvant

Biomarkers

Clinical Models
Adjuvant Rx space in solid tumors

Incompletely effective (high quality) surgery

WHO??

Completely effective systemic Rx
### Prognostic Biomarkers in ccRCC

<table>
<thead>
<tr>
<th>Clinicopathologic factors</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG PS</td>
<td>4.610 (2.077-10.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T classification</td>
<td>2.889 (1.918-4.352)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.234 (1.147-1.329)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fuhrman grade</td>
<td>2.073 (1.215-3.537)</td>
<td>0.008</td>
</tr>
<tr>
<td>UISS group</td>
<td>5.032 (2.856-8.865)</td>
<td>&lt;0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Molecular markers</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>p53</td>
<td>1.042 (1.020-1.065)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VEGF-D (epithelial)</td>
<td>0.980 (0.968-0.992)</td>
<td>0.002</td>
</tr>
<tr>
<td>VEGFR-1 (endothelial)</td>
<td>1.038 (1.014-1.063)</td>
<td>0.002</td>
</tr>
<tr>
<td>VEGFR-1 (epithelial)</td>
<td>1.017 (1.004-1.029)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ki-67</td>
<td>1.041 (1.004-1.079)</td>
<td>0.028</td>
</tr>
<tr>
<td>p21 (nuclear)</td>
<td>0.980 (0.962-0.999)</td>
<td>0.037</td>
</tr>
<tr>
<td>p27 (nuclear)</td>
<td>0.984 (0.966-1.002)</td>
<td>0.079</td>
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<tr>
<td>p56</td>
<td>1.009 (0.999-1.010)</td>
<td>0.087</td>
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<tr>
<td>CAXII</td>
<td>0.990 (0.978-1.002)</td>
<td>0.099</td>
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<tr>
<td>VEGF-A (epithelial)</td>
<td>1.009 (0.997-1.020)</td>
<td>0.158</td>
</tr>
<tr>
<td>EpCAM</td>
<td>0.987 (0.969-1.006)</td>
<td>0.173</td>
</tr>
<tr>
<td>p21 (cytoplasmic)</td>
<td>0.979 (0.942-1.016)</td>
<td>0.263</td>
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<tr>
<td>VEGF-D (endothelial)</td>
<td>0.835 (0.600-1.162)</td>
<td>0.286</td>
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<tr>
<td>Gelsolin</td>
<td>1.005 (0.996-1.011)</td>
<td>0.312</td>
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<tr>
<td>pAkt (nuclear)</td>
<td>0.990 (0.969-1.011)</td>
<td>0.340</td>
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<tr>
<td>VEGF-A (endothelial)</td>
<td>1.007 (0.993-1.021)</td>
<td>0.350</td>
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<tr>
<td>VEGF-C (epithelial)</td>
<td>1.007 (0.993-1.021)</td>
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<tr>
<td>Vimentin</td>
<td>1.006 (0.993-1.019)</td>
<td>0.358</td>
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<tr>
<td>CXCR3</td>
<td>0.996 (0.984-1.008)</td>
<td>0.497</td>
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<tr>
<td>pAkt (cytoplasmic)</td>
<td>1.004 (0.992-1.016)</td>
<td>0.535</td>
</tr>
<tr>
<td>VEGFR-3 (endothelial)</td>
<td>1.003 (0.991-1.016)</td>
<td>0.612</td>
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<tr>
<td>VEGFR-2 (epithelial)</td>
<td>1.003 (0.992-1.014)</td>
<td>0.613</td>
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<tr>
<td>CAIX</td>
<td>1.003 (0.991-1.015)</td>
<td>0.651</td>
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<tr>
<td>PTEN</td>
<td>1.003 (0.990-1.016)</td>
<td>0.653</td>
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<tr>
<td>VEGF-C (endothelial)</td>
<td>1.006 (0.977-1.036)</td>
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<td>p27 (cytoplasmic)</td>
<td>0.995 (0.966-1.024)</td>
<td>0.723</td>
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<tr>
<td>VEGFR-3 (epithelial)</td>
<td>1.005 (0.973-1.037)</td>
<td>0.778</td>
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<tr>
<td>VEGFR-2 (endothelial)</td>
<td>1.004 (0.971-1.038)</td>
<td>0.816</td>
</tr>
<tr>
<td>HIF-1α</td>
<td>0.999 (0.985-1.013)</td>
<td>0.909</td>
</tr>
</tbody>
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**Cancer Epidemiol Biomarkers Prev 2009;18(3). March 2009**

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**Genome-Wide Promoter Methyloome of Small Renal Masses**

Ilsiya Ibragimova¹, Michael J. Slifker², Marie E. Maradeo³, Gowrishankar Banumathy⁴, Essel Dulaimi², Robert G. Uzzo⁶, Paul Cairns¹*.

MicroRNA expression signatures of stage, grade, and progression in clear cell RCC.

Gowrishankar, Ibragimova, Zhou, Slifker, Devaraian, Al-Saleem, Uzzo and Cairns
### Risk Models for “Localized” RCC

<table>
<thead>
<tr>
<th>Model</th>
<th>Presentation</th>
<th>Reported/Externally validated C-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>UISS N=814</td>
<td>KM estimates</td>
<td>0.73/0.64-0.86</td>
</tr>
<tr>
<td>MSKCC* N=701</td>
<td>Nomogram</td>
<td>0.82/0.79-0.82</td>
</tr>
<tr>
<td>SSIGN N=1801</td>
<td>Points based algorithm</td>
<td>0.84/0.76-0.88</td>
</tr>
<tr>
<td>Leibovich* N=1671</td>
<td>Points based algorithm</td>
<td>0.82/0.7-0.86</td>
</tr>
<tr>
<td>Karakiewicz N=2474/2530</td>
<td>Nomogram</td>
<td>0.89/0.75-0.91</td>
</tr>
<tr>
<td>Yaycioglu</td>
<td>Formula</td>
<td>0.65/0.63-0.70</td>
</tr>
<tr>
<td>Condolo</td>
<td>Formula</td>
<td>0.67/0.63-0.75</td>
</tr>
</tbody>
</table>

1. **TNM stage**
2. **Nuclear Grade**
3. **Tumor Size**
4. **Performance Status**
5. **Presentation (symptoms)**
6. **Age**
7. **Gender**
8. **Coagulative necrosis**

All models retrospective

* Localized pts only
## Risk Models for “Localized” RCC

<table>
<thead>
<tr>
<th>Model</th>
<th>1° outcome</th>
<th># events in NoMo patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC*</td>
<td>RFS</td>
<td>72</td>
</tr>
<tr>
<td>Leibovich*</td>
<td>MFS</td>
<td>479</td>
</tr>
<tr>
<td>Karakiewicz</td>
<td>RCC specific survival</td>
<td>?</td>
</tr>
<tr>
<td>SSIGN</td>
<td>CSS</td>
<td>?</td>
</tr>
<tr>
<td>UISS</td>
<td>OS</td>
<td>14</td>
</tr>
</tbody>
</table>

565 “events” in NoMo patients predicted by these models
Eligibility for most recent adjuvant RCC RCT based on these predictive tools

$n \pm 10,000$ pts accrued
Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

1. Timing (and clonality)

2. Technique
   a. Node dissection
   b. Margin status

3. Toxicity

4. Tenacity
TIMING
(and clonality)

OR
Timing of Adjuvant Rx

Micrometastases (CTCs) (Halstedian)

- Clinical Stage 1
- Clinical Stage 2
- Clinical Stage 3
- Subclinical Stage IV/ Clinical Stage IV

Adjuvant Rx

CTCs

$0 \text{ x } 1 \times 10^9 / \text{cm}^3$
How long is the process of micromets in RCC? 

Exceptionally variable!

A 1 cm tumor = 10^9 cells (billion) +/- 40 tumor doublings
Full Spectrum “omic” Heterogeneity

DNA | RNA | Proteins | Metabolites

epi | kinome | cancer

Courtesy of Jonathan Chernoff, MD, PhD.
Surgical Issues in Timing/eligibility for Adjuvant Trials

Is this patient surgically eligible for an adjuvant trial?

- Patient with partial nephrectomy 3 yrs prior

- Tumor recurrence in residual kidney with local LN metastasis and soft tissue metastasis (fat tissue)

Does the renal recurrence represent:
Local persistence?
Primary recurrence?
Persistent multifocal?
New event?

Which is the N+ metastasis from? What about the soft tissue clone?

Who’s call is it??
Surgical Implications

• The Role of lymphadenectomy?

• The Role of cytoreduction or metastasctomy?

• The Role of neoadjuvant or adjuvant Rx???
TIMING
(and clonality)

AND

AND
Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

Technique:

- Node dissection

- Margin status
  Venous margins/partials/other
Surgical Progress in Advanced RCC

• We have debated role of lymphadenectomy

  – Conclusions ....

  • We have defined how poor N+ disease is
  • We don’t do enough LNDs (we think)
  • We refined “at risk” populations
  • We debate if lymphadenectomy is diagnostic or therapeutic (and have failed to answer the question)

• We have not changed OS
Radical Nephrectomy with and without Lymph-Node Dissection for T1 RCC

*EORTC 30881*

If cNo...
then <5% were pN1
implying you don’t need to do LN dissection

**Fig. 1 – Overall duration of survival.** O: number of deaths; n: total number of patients; LN Dis: lymph node dissection.
Lymphadenectomy?...NO

*High Risk No or N1 RCC Patients*

- N=606/1797 (34%) RN for Mo RCC had LND at Mayo Clinic 1990 – 2010
- N=111 (6.2%) N+
- 1:1 Propensity matching – no difference in DSS, OS

*Fig. 1 – Association of lymph node dissection (LND) with (A) cancer-specific survival among the subset of 370 propensity-score matched pairs and with (B) overall survival among the subset of 370 propensity-score matched pairs.*

*Gershman et al: Euro Urol, 2016*
Surgical Principles

20. For patients who are undergoing surgical excision of a renal mass with clinically concerning regional lymphadenopathy, physicians should perform a lymph node dissection for staging purposes. (Expert Opinion)

If suspicious lymphadenopathy is identified on imaging or during surgical exploration, a lymph node dissection (LND) should be performed primarily for staging and prognostic purposes. Selective performance of LND for patients who may have locally advanced disease can also be considered for staging purposes. Recent studies have been unable to confirm a survival benefit for LND for RCC. If lymph node involvement is confirmed on final pathology, medical oncology consultation should be considered. Level-1 evidence has contributed to strong consensus that LND need not be performed in patients with localized kidney cancer and clinically negative nodes.
Lymphadenectomy during Surgery for high risk RCC: Results from ASSURE Trial

36% of pts (701/1943) underwent LND in ASSURE
- All with cN+ and 30% of those with cNo
- 23% pN+
- Average LN yield n=3 (IQR 1-8) without an agreed upon template
- No increase in complications
- No improvement in OS/DFS observed in placebo vs adjuvant arms of cNo, pNo or pN+

Ristau, Haas and Uzzo et al., J Urol. July 2017
Margin Status...R0 vs R1

(R2 less of a concern)

• A combination of what the surgeon “sees” and what the pathologist “sees”
  – Lack of standardization re:
    • role of frozen section
    • inking process
    • Intraoperative communication
    • Extent of margin sampling (surgical AND pathological)

• Lack of evidence that microfocal margins “matter” for low risk disease
  – Implications for high risk disease??

• Biologically relevant margins??
  – Does fat = parenchymal = vascular??

• Reporting venous margin
Where we're heading...
Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

Toxicity:

The surgical bar is high!!

ACS Calculator – *Lap* RNx

75 yo male
ASA II
Healthy
71”
230 lb

Serious complication = 5%
Any complication = 6%
LOS = 2 days

http://riskcalculator.facs.org
2017: AUA Guidelines/AHRQ: Complication Risks

Perioperative outcomes and harms

N=38 studies, 11,802 pts evaluated perioperative outcomes including:
- EBL, transfusions, conversions and LOS
- N=24 studies compared RNx to PNx

When considering specific harms, partial nephrectomy had higher rates of urologic complications (including renal abscess, ureteral injury, urine leak and subsequent interventions) when compared to radical nephrectomy (low strength of evidence) and thermal ablation (low strength of evidence). However, rates of minor and major complications were similar among all three treatment modalities. Thermal ablation had the lowest reported rates of

Figure E. Pooled comparisons of perioperative outcomes and harms for radical nephrectomy (RN) versus partial nephrectomy (PN) from studies that presented effect estimates as risk ratios

Pierozazio et al: 2016 AHRQ report
Toxicities of Systemic Therapies in RCC

- **mAb against VEGF**
  - Hypertension, proteinuria, poor wound healing

- **Tyrosine Kinase Inhibitors**
  - HTN, fatigue, hand foot syndrome, nausea, diarrhea
  - LV dysfunction, hypothyroid, stomatitis, hematopoietic

- **mTOR inhibitors**
  - Stomatitis, pneumonitis
  - Hyperlipidemia

- **Checkpoint inhibitors**
  - Autoimmune disorders

RCTs and systemic therapy complicate the surgical “episode” of care

…and people are…

………watching

………..measuring

…………grading “surgical” care
Most autoimmune toxicities are reversible with immunosuppression (steroids) – **Implications for surgery**

**Fig 2.** Kinetics of appearance of immune-related adverse event.
Autoimmune toxicities seen with checkpoint inhibitors

- Endocrinopathies
  - Hyper → Hypothyroid
  - Central adrenal insufficiency
- Pneumonitis
- Diarrhea / Colitis
- Rash
- Myositis
- Neurotoxicity
  - Guillain-Barré syndrome
  - Cranial Nerve Palsy
Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

Tenacity

Getting surgeons into an RCT mindset
Examples of successes in RCC

- ASSURE, STRAC, PROTECT, ATLAS, ARISER etc….

- “ADAPT Trial” (AGS-007 - Argos Therapeutics)
  - Phase 3 Open-Label Randomized Study
  - Cytoreductive NTX followed by Sunitinib vs Sunitinib + AGS-003
    - Largest cytoreductive NTX trial ever performed to date
    - N= 1133 nephrectomies to randomize 462 patients to treatment
      - SUO-CTC performed 712 (62% of total) nephrectomies and randomized 284 (61% of randomized pts) patients to treatment

7+ years to accrue n=246 patients in SWOG 8949 (1991 – 1998)
2.5 yrs to collect n = 1133 cytoreductive NTX specimens (Nov 2012 – July 2015)
Surgical Considerations (impediments) for (neo)adjuvant Therapy Trials in RCC

1. Risk tools (models) are poor

2. Timing (and clonality) = undefined
   - “a chance to cut is a chance to cure”

3. Technique = non standardized

4. Toxicity = a concern

5. Tenacity = an evolving culture of RCTs