Innovative Thinking for Locally Advanced Kidney Cancer

(for Patients)

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## Disclosure

<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
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<tbody>
<tr>
<td>Consultant / Ad Board</td>
<td>Pfizer, GSK, Argos, Janssen, Urogen</td>
</tr>
<tr>
<td>Research, Data Monitor</td>
<td>Novartis, J &amp; J</td>
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</table>
What is Locally Advanced RCC?

- Tumor involving the:
  - Perinephric fat
  - Renal Sinus Fat
  - Renal Vein
  - Inferior Vena Cava
  - Nearby lymph Nodes
  - Adjacent organs
    - Adrenal, pancreas, colon, spleen or musculature on the left
    - Adrenal, liver, colon or musculature on the right
Clinical vs Pathological Staging: cTNM vs pTNM

Stage I
- Tumor <7 cm in greatest dimension and limited to kidney; 5-year survival, 95%

Stage II
- Tumor >7 cm in greatest dimension and limited to kidney; 5-year survival, 88%

Stage III
- Tumor in major veins or adrenal gland, tumor within Gerota’s fascia, or 1 regional lymph node involved; 5-year survival, 59%

Stage IV
- Tumor beyond Gerota’s fascia or >1 regional lymph node involved; 5-year survival, 20%
Why is Locally Advanced RCC Concerning?

- Risk of Micrometastatic Disease:
  - Timing of microscopic spread unclear and not measureable
  - Implies that the tumor will recur at some time in the future

- Currently believe that all metastases evolve from prior micrometastases that have been present yet undetectable or “suppressed”
Tumor Progression Paradigms
(evolution of micrometastases)

* driver (truncal) mutations

Surgery
then systemic Rx

Clones/subclones

Neoadjuvant Rx + surgery

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Timing of Perioperative Systemic Rx

Micrometastases (CTCs) (Halstedian)

Clinical Stage 1

Clinical Stage 2

Clinical Stage 3

Subclinical Stage IV/ Clinical Stage IV

0 1 x 10^9/cm^3

(Neo) Adjuvant Rx

CTCs
Timing of Perioperative Systemic Rx
Micrometastases (CTCs) (Fisheresque – NSABP)

Sub clinical Stage IV / Clinical Stage IV
Clinical Stage 3
Clinical Stage 2
Clinical Stage 1

0 (Neo) Adjuvant Rx
1 x 10⁹/cm³

CTCs
Adjuvant/Neoadjuvant Therapy

*Elusive*

The Holy Grail of Surgery

Incompletely effective (high quality) surgery

Completely effective systemic Rx
We all struggle ....

to advise the right treatment for locally advanced and mRCC
in the right patient
at the right time
Locally Advanced or mRCC…

- 71 yo and very healthy
- Good Renal Function

Reasonable experts can disagree... and defend

Where and Who
the patient sees first
Surgical Outcomes – pT3aNoMo ccRCC

• 71 yo and very healthy

• Good Renal Function

Karakiewicz et al: JCO 2007
Surgical Outcomes – pT3aN1Mo ccRCC

- 71 yo and very healthy
- Good Renal Function

Karakiewicz et al: JCO 2007
Past State (prior to 2006)

Incompletely effective surgery vs incompletely effective systemic Rx
Present State
Incompletely effective surgery vs more effective systemic Rx

Surgery perceived as playing offense
Systemic therapy perceived as playing defense
Hypotheses (Rationale) of RNx
(for locally advanced or mRCC)

• Clonal Deletion
  • Potential for curative resection (Ro) in locally advanced disease
  • Decrease source of new metastases from primary

• Improved pharmacodynamics
  • Drugs don’t get into necrotic tumors

• Primary tumors are immunosuppressive and pro-angiogenic
  • Rare spontaneous regressions

• Symptomatic relief

It’s “aggressive therapy”...
(and that is perceived as better)
Guidelines for Perioperative Systemic Rx in RCC:

- Adjuvant Space (n=8076)
  - Reported Level 1 data from ASSURE, S-TRAC, PROTECT, ATLAS
  - Fully accrued trials SORCE and EVEREST

- Neoadjuvant Space
  - No mention in guidelines
Cancer is an evolving ecosystem
A  Biopsy Sites

R1 (G3)  R2 (G3)
R3 (G4)  R4 (G1)
R5 (G4)  R6 (G1)
R7 (G4)  R8 (G4)
R9        

10 cm

Hilum

B  Regional Distribution of Mutations

<table>
<thead>
<tr>
<th>Ubiquitous</th>
<th>Shared primary</th>
<th>Shared metastasis</th>
<th>Private</th>
</tr>
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Gerlinger et al, NEJM 2012
- 95 cancer biopsies from 33 pts with ccRCC
  - Average of 7,680 unique somatic substitutions and 1,193 indels per patient

- Driver event is loss of 3p loss (40Mb segment) occurs decades before diagnosis
  - Loss of 4 tumor suppressors = VHL (70-80%), PBRM1 (40%), BAP1 (10%), SETD2 (10%)
  - Simultaneous 5q gain through chromothripsis where 40% resulted in t(3;5)
  - Initial clonal expansion of only a few hundred cells with long latency

- Inactivation of second VHL allele leads to clonal evolution down multiple pathways
Branched Evolution (Clone Chasers)

Heterogeneity as a Hallmark

Selective Intrinsic Pressures (stochastic)

Variable Latency

Clonal Evolution
- linear vs branched vs punctated
- selective sweeps

Failure to recognize/repair/rescue

Metastatic Cascade
- migration/invasion
- intravasation/extravasation
- colonization/proliferation

Selective Extrinsic Pressures = Rx

**Cancer Specific Death**
Intratumor heterogeneity

Genomic instability (SCNA)

Example Trees

DRIVERS

VHL

Mono

PBRM1→ SETD2

PBRM1→ SCNA

PBRM1→ PI3K

Multiple Clonal

BAP1

VHL

Wild Type
## Intratumoral Heterogeneity

<table>
<thead>
<tr>
<th>Genomic Instability (SCNA)</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td><img src="image1.png" alt="Image of high genomic instability" /></td>
<td><strong>RAPID PROGRESSION</strong></td>
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<tr>
<td><strong>ATTENUATED PROGRESSION</strong></td>
<td>+++</td>
<td><strong>LOW PROGRESSION</strong></td>
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<tr>
<td><strong>Low</strong></td>
<td><img src="image3.png" alt="Image of low genomic instability" /></td>
<td><img src="image4.png" alt="Image of low progression" /></td>
</tr>
<tr>
<td><strong>ATTENUATED PROGRESSION</strong></td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

### Intratumoral Heterogeneity

- **High:***
  - Genomic Instability (SCNA): High
  - Progression: Attenuated

- **Low:***
  - Genomic Instability (SCNA): Low
  - Progression: Attenuated

- **RAPID PROGRESSION:***
  - Genomic Instability (SCNA): High
  - Progression: Rapid

- **LOW PROGRESSION:***
  - Genomic Instability (SCNA): Low
  - Progression: Low
## Intratumoral Heterogeneity

<table>
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</tr>
<tr>
<td>Low</td>
<td>![Low Low]</td>
<td>![High Low]</td>
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</table>
Tumor Biology is King

(but we don’t fully understand it)
Basic Principles in Surgical Oncology

Blake Cady, MD

Presented at the 77th Annual Meeting of the New England Surgical Society, Dixville Notch, NH, September 27, 1996.

Case Selection is Queen
SWOG 8949: Cytoreductive Nephrectomy Improves Survival.....in patients with good performance status

**Benefit of Nx mainly in ECOG 0 patients**

**N** | **Deaths** | **Median**
--- | --- | ---
No Surg/PS = 0 | 50 | 46 | 12
No Surg/PS = 1 | 71 | 69 | 5
Surg/PS = 0 | 66 | 57 | 17
Surg/PS = 1 | 54 | 49 | 7

Flanigan et al NEJM: 345, 2001
## Surgical Risk Calculator

### Procedure:
50230 - Nephrectomy, including partial nephrectomy, any open approach including rib resection; radical, with regional lymphadenectomy and/or venous caval thrombectomy.

### Risk Factors:
- 65-74 years
- Male
- Partially dependent functional status
- Malignant systemic disease
- Disseminated cancer
- Diabetes (Oxid)
- HTN, Class I Obesity

### Outcomes
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Your Risk</th>
<th>Average Risk</th>
<th>Chance of Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Complication</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Any Complication</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Cardiac Complication</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Surgical Site Infection</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Readmission</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Return to OR</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Death</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Discharge to Nursing or Rehab Facility</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Septic Complication</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Predicted Length of Hospital Stay:** 6.5 days

### How to Interpret the Graph Above:
- Your Risk
- Average Patient Risk
- Your % Risk

### Surgeon Adjustment of Risks
This will need to be used infrequently, but surgeons may adjust the estimated risks if they feel the calculated risks are underestimated. This should only be done if the reason for the increased risks was NOT already entered into the risk calculator.

1. No adjustment necessary

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Therapies are the Prince and Princess who occasionally try to usurp the throne ...
but current therapies often fail to overcome the powerful forces of the King and the Queen.
Clinical Trials
Improve Decision Making...

Can address the known knowns...

... but cannot completely remove uncertainty
In the Absence of Certainty: *Prospect Theory*

Philosophy and Perspective Matter

1. Simplify Choices
2. Frame the Decision
3. Estimate probability


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Perspective Contextualizes and Validates Approach

Effective Systemic Therapy

Level 1 data

Validates pt/MD perspectives

SOC and population based data

Systemic Rx not curative

Validates pt/MD perspectives

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Carmena does put an end to unnecessary Cytoreductive Nephrectomy. So I struggle less... to advise the right treatment for mRCC in the right patient at the right time, selection will become easier.

Unbiased judgment and surgical excellence are Prince and Princess. Biology is King.

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