It’s not a four legged animal anymore

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Disclosure

• No disclosures
Four legged animal which use the tips of their toes, usually hoofed, to sustain their whole body weight while moving.

Goals

• What translates in the terms of clinical outcomes after histopathological and molecular diagnosis.

• Pathological information specifically being looked at by clinical researchers.
Prostate cancer-Clinical case

• 78 year old presented to PCP with urinary complaints and PSA of 2.69
• Prostate exam showed a nodule
• Urologist performed a biopsy shows
PET scan shows fine needle aspiration of bone and liver confirmed as small cell carcinoma.

Treatment

- Patient received 6 cycles of carboplatin and etoposide. And scan shows
Prostate cancer

- Small cell prostate cancer and neuroendocrine differentiation: - Peculiarities
  1. Androgen receptor negative- Does not respond to androgen deprivation.
  2. Will not respond to androgen withdrawal- Similarly prostate adenocarcinoma respond to withdrawal of androgen deprivation
  3. Respond to platinum and etoposide combination.- Adenocarcinoma response
  4. Rapidly progressive and fatal

What clinicians looking for

• What percentage of tissue has small cell component
• If tumor has neuroendocrine differentiation- is it high grade or low grade
• Clinical practice – Patient with biopsy of primary cancer shows mixed histology we request biopsy evaluation of metastatic site to evaluate which component is present in the metastasis

Clinical trials in Prostate Adenocarcinoma

• Trials targeting androgen receptor or its pathway -Patients with small cell or high grade neuroendocrine differentiation are excluded.
• Trials targeting PSMA - It may be important to differentiate between Gleason 10 and small cell carcinoma. PSMA is negative on these patients.
• Trials targeting novel therapy for adenocarcinoma in neoadjuvant setting will also rule out small cell or Sarcomatoid variants.
How many hooves

Kidney cancer- Non Clear cell

- Non Clear cell carcinoma- Papillary, Sarcomatoid variant, Collecting duct
- Poor response to immunotherapy.
- Underrepresented in clinical trial with VEGF and mTOR inhibitor.
- No clear therapy. And usually portends poor survival and outcomes
- Pathway appears to play a role, more so in type 1 papillary renal cell carcinoma.

(Upton, Parker et al. 2005) C-met
(Motzer, Bacik et al. 2002)
Papillary Carcinoma

• c-Met pathway plays a role in tumor-genesis more so in type 1.\(^1\)
• Epidermal growth factor and c-Met signal pathway cross talk. EGFR activation may lead to constitutive c-Met phosphorylation.\(^2\)
• Clinical trials are ongoing looking at both targets in this subset of tumors.

1.(Schmidt, Junker et al. 1999)
2.(Jo, Stolz et al. 2000)

S1107, "Parallel (Randomized) Phase II Evaluation of ARQ 197 and ARQ197 in Combination with Erlotinib in Papillary Renal Cell Carcinoma."
Eligibility Criteria

• Patients must have histologically or cytologically confirmed papillary histology renal cell carcinoma which is metastatic, or locally advanced and unresectable.
• Mixed histologies will be allowed provided that they contain ≥ 50% of the papillary component

Adjuvant treatment in kidney cancer

• Adjuvant immuno-chemotherapy fail to demonstrate any benefit in high risk disease after nephrectomy.①
• Immunotherapy alone showed worse outcomes in adjuvant settings.②

• 1. (Atzpodien, Schmitt et al. 2005)
• 2. (Clark, Atkins et al. 2003)
Adjuvant therapy clinical trials

- Nomograms exist which can predict recurrence of kidney cancer up to 12 years post nephrectomy.¹

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POSTOPERATIVE PROGNOSTIC NOMOGRAM FOR RENAL CELL CARCINOMA

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<th>20</th>
<th>30</th>
<th>40</th>
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<td>Tumor Size</td>
<td>0</td>
<td>2</td>
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<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
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<td>1997 p Stage</td>
<td>P3a</td>
<td>P3a</td>
<td>P3b</td>
<td>P4</td>
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<td>P4</td>
<td>P4</td>
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<td>P4</td>
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<tr>
<td>60 Mo. Recurrence Free Surv.</td>
<td>0.98</td>
<td>0.96</td>
<td>0.94</td>
<td>0.9</td>
<td>0.85</td>
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<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
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</table>
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¹ (Kattan, Reuter et al. 2001)

Ongoing clinical trials

- **S0931**, “EVEREST: EVERolimus for Renal Cancer Ensuing Surgical Therapy, A Phase III Study.

![Flowchart diagram](image)
Inclusion criteria

- **Intermediate High Risk Group**
  - pT1b G3-4, N0 (or pNX where clinically N0), M0 (>4cm)
  - pT2a-b G1-2, N0 (or pNX where clinically N0), M0
  - pT2a-b G3-4, N0 (or pNX where clinically N0), M0
  - pT3a G1-2, N0 (or pNX where clinically N0), M0

- **Very High Risk Group**
  - Microvascular invasion of the renal vein of pT1a-pT3a (as long as pT3a is Grade 1-2) N0 (or pNX)
  - where clinically N0) M0
  - pT3a G3-4, N0 (or pNX where clinically N0), M0
  - pT3b-c G any, N0 (or pNX where clinically N0), M0
  - pT4 G any, N0 (or pNX where clinically N0), M0
  - pT any G any, N+ (fully resected), M0
  - Microvascular invasion of the renal vein with above other characteristics

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Relation of microvessel density with microvascular invasion, metastasis and prognosis in renal cell carcinoma

Esin Yildiz, Semih Ayan*, Fahrettin Goze, Gokhan Gokee* and Emin Y. Gultekin*, Departments of Pathology and Urology, Cumhuriyet University, Sivas, Turkey

- Presence of MVI appears to be a marker for identifying patients with an adverse prognosis.
Exclusion criteria

- Collecting duct or medullary carcinomas
- Positive renal vein margins are eligible unless there is invasion of the renal vein wall at the margin (provided no other margins are positive).

Size and the skin color
High grade undifferentiated tumors

- Rule out lymphoma and germ cell tumors

(Slamon, Leyland-Jones et al. 2001)
Her-2 positive breast cancer

- 20 percent of breast cancers overexpress human epidermal growth factor receptor 2 (HER2),
- Transmembrane glycoprotein epidermal growth factor receptor (EGFR) with tyrosine kinase activity.
- Historically, overexpression of this receptor was associated with an increased risk of disease recurrence and an overall worse prognosis

IHC criteria by ASCO/CAP guidelines

- IHC3+ if there is complete and intense circumferential membrane staining within >10 percent of tumor cells.
- IHC2+ if (1) there is incomplete and/or weak/moderate circumferential membrane staining within >10 percent of tumor cells, or (2) complete and intense circumferential membrane staining within <10 percent of tumor cells. All IHC 2+ tumors are reported as HER2 equivocal

FISH criteria

*ISH is defined as the ratio between HER2 and the chromosome 17 enumeration probe (CEP17).*

*Results are reported as:*

- ISH positive if the HER2/CEP17 ratio $\geq 2.0$, regardless of the average HER2 copy number signals/cell.
- ISH positivity also includes a HER2/CEP17 ratio $< 2.0$ if the average HER2 copy number $\geq 6.0$ signals/cell.

Her-2 positivity not only for breast but also for stomach and esophageal

Figure 2 (A) Median overall survival and (B) progression-free survival in the primary analysis population HR=hazard ratio.

Yung-Jue Bang, Eric Van Cutsem, Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, etc.

*Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial*

The Lancet, Volume 376, Issue 9742, 2010, 687 – 697

http://dx.doi.org/10.1016/S0140-6736(10)61121-X
• (Ruschoff, Hanna et al. 2012)

CD30 positive Hodgkin or Testicular cancer
• Patients with advanced testicular cancer not responding platinum based first line and second line therapy

Antitumor activity of brentuximab vedotin in CD30 positive refractory germ cell tumors.
Costantine Albany MD  Abstract 327 ASCO GU2013

Large cell Ca of the lung is not enough
Kaplan-Meier overall survival and progression-free survival (PFS) curves for the entire population, patients with nonsquamous histology (adenocarcinoma plus large cell), and patients with squamous histology.

Scagliotti G V et al. JCO 2008;26:3543-3551

Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer

Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D.,
(A) Kaplan-Meier estimates of progression-free survival according to biomarker status and treatment arm.

Cumulative five-year disease-specific survival rates for GISTs classified as risk level I through

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Tumor Size</th>
<th>Mitotic rate</th>
<th>DFS at 5 years</th>
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<tbody>
<tr>
<td>I</td>
<td>≤5 cm</td>
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<td>&lt;5 cm</td>
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<td>&gt;10 / 50 HPF</td>
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<td>6-10/50 HPF</td>
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</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>&lt;5/50 HPF</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>&gt;5 cm</td>
<td>&gt;10/50 HPF</td>
<td>25%</td>
</tr>
</tbody>
</table>
Lymph nodes in resected specimen

- As per NCCN minimal number of lymph nodes reported in the path specimen should be 12, otherwise further analysis of specimen should be performed.

Microsatellite instability

- High levels of DNA microsatellite instability (MSI-H), defined as instability in ≥30 percent of microsatellite loci. (Thibodeau, Bren et al. 1993)
- Clinical relevance in making treatment decisions
- Better prognosis
- Adjuvant 5-FU-based chemotherapy is less beneficial

Four legged animal with no hooved feet and an odd number of toes on each foot, as well as mobile upper lips and a similar tooth structure and can carry humans for pleasure.

Thank you