The role of metastatectomy and additional therapy in kidney cancer

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Case Presentation

• 62 year old man underwent CT scan after auto collision, and found to have 8 cm kidney tumor.
• Underwent nephrectomy
Case Presentation

• No evidence of disease following surgery
• Five years later:
  • 2 cm RLL lung nodule on surveillance CT scan.
  • Feeling well.
CASE PRESENTATION: What to do next?

LOCAL THERAPY?

SYSTEMIC THERAPY?

OBSERVATION?
DEFINITION: Surgery to remove cancer beyond the primary site
Can be performed at the time the primary is removed or Years later

RATIONALE:
• Alleviate or prevent local symptoms
• Control the cancer: Help the patient live longer with good quality of life
• Obtain tissue for molecular analysis
METASTASECTOMY

• Control the cancer: *Help the patient live longer with good quality of life*

• 1. Avoid systemic treatment and its potential toxicities

• or

• 2. Follow up with systemic treatment: Delay the development of resistant clones
METASTASECTOMY

SHOULD WE DO IT?

Do the risks of the operation outweigh the benefit from removing the visible cancer?
ANCIENT HISTORY OF SURGERY FOR CANCER

400 BC  Hippocrates describes the stages of cancer and advises against surgery for advanced disease¹
Does Metastasectomy help patients?

How do we know?

Randomized Clinical Trial ???
Does Metastasectomy help?

How do we know?

Randomized Clinical Trial

PERSONAL EXPERIENCE
EXPERT OPINION
METASTASECTOMY

SHOULD WE DO IT?

WHO WILL BENEFIT?

All patients are not the same

How can we tell?
METASTASECTOMY-WHAT FACTORS PREDICT LONGER TIME UNTIL RECURRENCE?

NUMBER OF METASTATIC SITES

DISEASE-FREE INTERVAL

2019: No set “formula” or highly evidence-based approach. Treatment is individualized based on clinical features, MD experience and patient preference.
Case Presentation Continued

- 62 year old man underwent nephrectomy for T3a ccRCC 5 years ago.
- CT now: 2 cm RLL lung nodule
- Nodule Resected
- No evidence of disease following surgery
- Medical oncologist recommends close follow up

- Thoracic Surgeon is FURIOUS that no systemic treatment is offered after the operation... 😞
The Metastasectomy Dilemma

• Metastasectomy has been performed for mRCC for over 80 years.
  • Synchronous: at time of nephrectomy; Metachronous: later

• Risk of recurrent disease is high

• No systemic therapy has been shown to improve outcomes in patients NED after metastasectomy: UNMET NEED
A randomized, open label, multicenter phase 2 study, to evaluate the efficacy of Sorafenib in patients with advanced Renal Cell Carcinoma (RCC) after a radical resection of the metastases: RESORT trial.

Giuseppe Procopio¹, Francesco Cognetti², Rosalba Miceli¹, Michele Milella², Alessandra Mosca³, Vincenzo Chiuri⁴, Alessandra Bearz⁵, Franco Morelli⁶, Cinzia Ortega⁷, Francesco Atzori⁸, Maddalena Donini⁹, Raffaele Ratta¹, Antonella Martinetti¹, Rosanna Montone¹, Filippo de Braud¹, Vera Cappelletti¹, Elena Verzoni¹

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RESORT: Study Design

Key eligibility criteria:
- Hystological diagnosis of predominantly clear cell RCC
- Maximum 3 metastatic lesions (independently of the site)
- Absence of radiological residual lesions following surgical removal of metastatic disease
- Histologically proven disease free margins of resected surgical specimen
- No more than three months from radical resection of metastases
- ECOG Performance Status of 0-2

Randomized:
1:1

Stratification according to:
- Time from nephrectomy (> or < 12 months)
- Site of disease (lung vs other)
- Number of lesions (single vs multiple)

Primary endpoint:
RFS

Secondary endpoints:
OS
Safety profile

Exploratory endpoints:
Translational analyses on blood and tumor samples

Sorafenib* for 52 weeks
Observation for 52 weeks

*Starting dose: Sorafenib 400 mg once a day for 3 weeks. After 21 days the dose should be increased to the standard dose (400 mg bid) if the patient has not experienced greater than Grade I skin toxicity or greater than Grade II of any other toxicity.

RFS, Recurrence Free Survival
OS, Overall Survival

Presented By Giuseppe Procopio at 2018 ASCO Annual Meeting
mRFS in the two treatment arms

<table>
<thead>
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<th>n. of pts*</th>
<th>n. of events</th>
<th>median (months)</th>
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<tr>
<td>arm= OBS**</td>
<td>36</td>
<td>12</td>
<td>35.0</td>
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<tr>
<td>arm= SORAFENIB</td>
<td>32</td>
<td>14</td>
<td>29.0</td>
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<tr>
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<th>12 months RFS (%)</th>
<th>24 months RFS (%)</th>
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<tbody>
<tr>
<td>arm= OBS**</td>
<td>74 (59-91)</td>
<td>59 (42-82)</td>
</tr>
<tr>
<td>arm= SORAFENIB</td>
<td>62 (46-84)</td>
<td>52 (35-76)</td>
</tr>
</tbody>
</table>

* pts, patients
** OBS, observation
Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: A trial of the ECOG-ACRIN cancer research group (E2810)


UPMC Hillman Cancer Center, Pittsburgh, PA; Dana Farber Cancer Institute, Boston, MA; City of Hope Comprehensive Cancer Center, Duarte, CA; Emory University School of Medicine, Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Mayo Clinic, Rochester, MN; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; University of Illinois College of Medicine, Chicago, IL; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer Center, Iowa City, IA; University of Kansas Cancer Center, Westwood, KS; University of Kansas, Kansas City, KS; Our Lady of Mercy Cancer Center, New York, NY; University of Kentucky, Lexington, KY; Penn Medicine Abramson Cancer Center, Philadelphia, PA; Sidney Kimmel Cancer Center At Johns Hopkins, Baltimore, MD
Pazopanib

- **Pazopanib** has been a standard of care for first-line systemic therapy for metastatic RCC based upon improved progression-free survival (PFS) compared to placebo (**Sternberg et al.** 2010). PFS was non-inferior vs. sunitinib and **favorable patient reported outcomes** (**Motzer et al.** 2013).

- Utility of VEGF-targeted agents in the NED (adjuvant or post-metastasectomy) state was unknown at study conception.
E2810 Hypothesis

12 months of pazopanib treatment will increase disease-free survival in patients with metastatic RCC who have been rendered radiographically disease free by surgical metastasectomy
**E2810 STUDY SCHEMA**

- **RCC M1 Resected To NED**
- **No Prior Systemic Therapy**

**RANDOMIZATION Stratification:**
- DFI < or > 1yr
- 1 or > 1 site resected

**Endpoints**
- DFS
- OS
- AEs
- PROs
- Lab Correl.

**Pazopanib 800 mg qd**

**Placebo 800 mg qd**

**52 weeks Rx**

**CT q3mo**

DFI: disease-free interval  
DFS: disease-free survival  
PRO: patient reported outcome

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Pazopanib did not improve disease-free survival

Leonard J. Appleman MD PhD

Medians: 14.2, 17.3

HR (pazopanib vs placebo) [95% CI] = 0.85 [0.55, 1.31]
Pazopanib did not improve disease-free survival

Median follow up - 30 months
83/129 DFS events (64%)

36 month DFS:
Pazopanib 26%
Placebo 22%
(estimated 25% at start of study)
OUTCOMES AFTER METASTASECTOMY MEDIAN VS. “TAIL OF THE CURVE”

"This is a personal story of statistics..."

THE MEDIAN ISN'T THE MESSAGE
by Stephen Jay Gould

Born in 1941, Stephen Jay Gould was a geologist, zoologist, paleontologist and evolutionary biologist at Harvard. He was also one of the most noted, prolific and best-selling scientific writers of our day. He was diagnosed in 1982 with abdominal mesothelioma, a rare and very deadly form of cancer associated with exposure to asbestos. This is his story. It was first published in Discover magazine in June 1985 and was reprinted here at Phoenix5 with his kind permission. He beat the cancer for 20 years, finally passing on May 20, 2002, giving all of us a valuable lesson in beating the odds.

Ribas, Hersey, Middleton, Gogas, Flaherty, Sondak, Kirkwood 2012
Trend toward improved disease-free survival for disease-free interval > 1 year

The HR for > 1 yr. versus ≤ 1 yr. = 0.55 (0.35, 0.87)
log rank p-value = 0.01
DFS by Stratification Factor: Number of Resected Sites

- Red line: 1 resected site (66 events/103 cases)
- Blue line: >1 resected sites (17 events/26 cases)

Probability of DFS vs. Months from registration.
One third of patients with renal cell carcinoma present with metastatic disease

**Hypothesis**: removal of primary tumor will be beneficial
Because…

1. Alleviation of tumor-mediated immune suppression
Two Randomized studies: Newly diagnosed metastatic RCC with primary in place:

Interferon-α2b* vs. Cytoreductive nephrectomy followed by Interferon-α2b

SWOG (n=241) and EORTC (n=83); 1990s

*Median PFS 5-6 months. Response rate 6%. Significant chronic and constitutional toxicity
Cytoreductive nephrectomy +IFN vs IFN Alone: Combined SWOG/EORTC OVERALL SURVIVAL

HR 0.67 (Median 13.6 v 7.8 months)
1990s-2006
Interferon-a2b

2006-2013
Targeted Rx
Sorafenib, sunitinib, temsirolimus, everolimus, pazopanib, axitinib, bevacizumab, cabozantinib
Is there a benefit to cytoreductive nephrectomy for patients treated with targeted therapy against VEGF and other pathways?
Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Heng et al. Overall Survival

Only for pts with 1, 2 or 3 out of 6 possible IMDC risk factors
Heng et al. Overall Survival

Only for pts with 1, 2 or 3 out of 6 possible IMDC risk factors
Only for pts with 1, 2 or 3 out of 6 possible IMDC risk factors

Overall Survival

RETROSPECTIVE
CARMENA: Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma (mRCC) - Results of a phase III non-inferiority trial. (NCT00930033)


On Behalf of Carmena investigators

Presented By Arnaud Méjean at 2018 ASCO Annual Meeting
CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

- Confirmed metastatic clear cell RCC / Biopsy
- ECOG-PS 0-1
- Amenable to nephrectomy
- Eligible for sunitinib
- Brain metastases absent/controlled by treatment
- No prior systemic therapy for RCC

Arm A
- Nephrectomy
- 3-6 weeks
- Sunitinib 50 mg QD 4 wks on / 2 wks off

Arm B
- Sunitinib 50 mg QD 4 wks on / 2 wks off

Stratification
- MSKCC risk group
- Center location

Primary endpoint: Overall survival
Secondary endpoints: Progression-free survival, objective response rate, clinical benefit, safety

LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma
Overall survival (ITT)


HR 95%CI = 0.89 (0.71-1.10)
Non inferiority study ≤1.20

Median follow-up was 50.9 months (range 0.0-86.6)
Progression free survival (ITT)

Presented By Arnaud Mejean at 2018 ASCO Annual Meeting

CN, cytoreductive nephrectomy; PFS, progression-free survival
CARMENA STUDY

• How should/will this change practice?

• Would be helpful to know about patients who were not considered for the study and went to surgery as standard of care because physician or patient preference (including outcomes).

• How to reconcile with IMDC data?
1990s-2006
Interferon-a2b

2006-2016
Targeted Rx
Sorafenib, sunitinib,
temsirolimus, everolimus,
pazopanib, axitinib,
bevacizumab, cabozantinib

2019-
PD-1 antibodies,
Combos
FUTURE DIRECTIONS

Metastasectomy and Immune checkpoint inhibitors

• Oligometastatic disease allowed in ongoing adjuvant randomized studies:

  • **PROSPER-RCC** (EA8143, NCT03055013) (metastasectomy allowed within 12 weeks of nephrectomy). (Nivolumab vs. observation; pre/post-op; L. Harshman, P.I.)
  • **KEYNOTE 564** (NCT03142334; Pazopanib vs. placebo (metastasectomy allowed within 1 year)
  • **IMmotion010** (NCT03024996; atezolizumab vs. placebo; metachronous or synchronous metastasectomy allowed)
EA8143 Study Update
A Phase 3 Randomized Study Comparing PERioperative Nivolumab vs. Observation in Patients with Localized Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER RCC)

Lauren Harshman, MD
EA8143 Study Chair
ECOG-ACRIN Fall Group Meeting
October 2018
Fort Lauderdale, FL
EA8143 PROSPER RCC: Adjuvant Therapy with a Twist

- Need the trifecta: presurgical priming with PD-1 blockade necessary for enhanced efficacy
- 1 adjuvant dose may not be sufficient → further engage with adjuvant therapy
- No Placebo—patients really do care about this!
ADDITIONAL LOCAL TREATMENT OPTIONS

• Radiation Therapy (including stereotactic radiation)
  • Kidney cancer not particularly sensitive to radiation but new techniques can achieve higher doses without damage to normal tissues

• Thermal energy techniques
  • Cryotherapy (tumor ice ball)
  • Radiofrequency ablation (kill it with fire!)
  • Embolization/chemoembolization
Future treatment paradigm?

• Pre-operative priming with immunotherapy (anti-PD-1)
• Surgery to remove metastasis
• Post-operative immunotherapy and close monitoring.
Medicine vs. Surgery
Medicine AND Surgery
(for some patients)
THANK YOU