Radiotherapy in Metastatic Urothelial Cancer and RCC

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Disclosures

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Varian, AstraZeneca, Janssen

Advisory/Consultancy roles:
Varian
Background
- Differential RT-sensitivity: Urothelial vs RCC

Clinical evidence
- Clinical indications and efficacy
- Primary vs Metastasis-directed therapy
- One size fit all? How aggressive with ablative RT?

Advanced radiotherapy techniques
- Technological advances: extracranial metastatic lesions
- Dose?

Future advances
- Combination with novel targeted therapeutics
- Combination with immunotherapy
Differential radiosensitivity between bladder/UC vs RCC

CANCER OF THE KIDNEY—RADIATION THERAPY AND ITS INDICATIONS IN NON-WILMS’ TUMORS

Jerome M. Vaeth, MD

Cancer, 1973

Radiation therapy occupies an important role in the management of malignant renal tumors. Presently, irradiation is utilized as a pre or postoperative adjunct to nephrectomy in potentially curable cases. Evidence is accumulating which indicates that there are fewer local recurrences and increased long-term survivals in irradiated patients. The use of ionizing radiations for palliation can be effective. In general the cancers are slowly responsive but display definite radiosensitivity, albeit delayed. Relatively high total doses of radiations are necessary to achieve tumor sterilization or even regression.

EFFICACY OF RADIOCHEMOTHERAPY WITH PLATIN DERIVATIVES COMPARED TO RADIOTHERAPY ALONE IN ORGAN-SPARING TREATMENT OF BLADDER CANCER

Rolf Sauer, M.D.,* Stefan Birkenhake, M.D.,* Reinhard Kühn, M.D.,† Christian Wittekind, M.D.,‡ Karl Michael Schrott, M.D.,‡ and Peter Martus, M.D.§

Initial response (remission rate)
TURB alone provided a complete remission (i.e., R0 = curative resection) in 20% (55 of 282 patients). The corresponding figures with additional RT were 57% (56 of 98) and 80% (145 of 181) after RCT. The CR rate of 85% (79 of 93) following RCT with cisplatin was superior to RCT with carboplatin which resulted in a 70% (48 of 69) complete remission rate (p = 0.02).
RT-sensitivity of RCC & UC

RCC
- Historically known to be “radioresistant”
- Some data on the use of RT in the neoadjuvant and adjuvant setting – But large doses are needed, at the expense of normal tissue toxicities
- Interestingly, normal renal tissue is extremely radiosensitive! – phenotype induced by tumour mutational profile?
- Clinical indication: Metastasis-directed therapy

UC
- Good responses with RT
- Radiosensitivity modulated by tumour biology such as hypoxia
- Tumours respond to conventional fractionated doses
- Can be enhanced by CDDP
- Clinical indication: Primary and Metastasis-directed therapy
Evidence for RT in bladder CA

Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer


- >80% response rates with newer RT techniques
- >75% Bladder-intact 5-y DSS
- 25% salvage cystectomy rates

RT offers good primary local control!
RT in M1 bladder cancer

Conventional clinical indications

- Local control
- Hematuria
- Pain (secondary to bulky tumour or invasion into the plexus)
- Other symptoms due to metastatic lesions

Dose

- Primary: 21 Gy/3# (BA09 study); 36 Gy/12#; 52.5 Gy/20# (better performing patients)
- Metastasis: (non-ablative doses) single 8 Gy, 20 Gy/5#; (ablative) 24 Gy/2#; 27-30 Gy/3#; 30-40 Gy/5#
High dose “radical” RT in M1 BC
Is there benefit beyond local palliation?

Efficacy of High-Intensity Local Treatment for Metastatic Urothelial Carcinoma of the Bladder: A Propensity Score–Weighted Analysis From the National Cancer Data Base


2016
- Screened >600,000 BC from NCDB
- HI local tx vs non-HI

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
High dose “radical” RT in M1 BC

Is there benefit beyond local palliation?

Efficacy of High-Intensity Local Treatment for Metastatic Urothelial Carcinoma of the Bladder: A Propensity Score–Weighted Analysis From the National Cancer Data Base

Table 3. Multivariable Logistic Regression Model That Predicts the Receipt of High-Intensity Local Treatment for Metastatic Urothelial Carcinoma of the Bladder in the Unweighted Study Population

Includes non-academic centres and cT3 tumours being less likely to receive HI local tx

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
High dose “radical” RT in M1 BC

Is there benefit beyond local palliation?

Includes non-academic centres and cT3 tumours being less likely to receive HI local tx

Cytoreductive vs Consolidative Local Tx
Suggests crucial for systemic tx as backbone of tx
HI Local tx may have value in carefully selected patients
High dose “radical” RT in M1 BC

Is there benefit beyond local palliation?

Radical Treatment of the Primary Tumor in Metastatic Bladder Cancer: Potentially Dangerous Findings From Observational Data

Christopher M. Booth, Queen’s University Cancer Research Institute, Kingston, ON, Canada
Safiya Karim, Queen’s University Cancer Research Institute, Kingston, ON, Canada
Yingwei Peng, Queen’s University Cancer Research Institute, Kingston, ON, Canada
D. Robert Siemens, Queen’s University Cancer Research Institute, Kingston, ON, Canada
Kelly Brennan, Queen’s University Cancer Research Institute, Kingston, ON, Canada
William J. Mackillop, Queen’s University Cancer Research Institute, Kingston, ON, Canada

HI Local tx may have value in carefully selected patients

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
Metastasis-directed therapy in RCC

Clinical indications
- Hematuria (Bulky primary)
- Pain (secondary to bulky tumour or invasion into the plexus)
- Cord compression

Dose
- Conventional notion that RCC is a “radioresistant” tumour
- Primary: 21 Gy/3#; 24 Gy/6#; limited evidence for large conventional (1.8-2.0 Gy/#) fractionated doses (>45-50 Gy)
- Metastasis: (non-ablative doses) single 8 Gy, 20 Gy/5#; (ablative) 24 Gy/2#; 27-30 Gy/3#; 30-40 Gy/5#
Oligometastatic vs Polymetastatic

- Distinct clinical trajectories
- Potential long-term survival
- More relevant in present era of TKI and immunotherapy
- Good retrospective single-institutional data

Hofmann, Eur Urol, 2005

Lu, Oncotarget, 2016
Oligometastatic RCC: distinct clinical entity

Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005–2014

M. Stenman\textsuperscript{a,*}, G. Sinclair\textsuperscript{b}, P. Paavola\textsuperscript{a}, P. Wersäll\textsuperscript{c}, U. Harmenberg\textsuperscript{c,1}, M. Lindskog\textsuperscript{a,1}

Long term survivors even at 10 y!!!
Oligometastatic RCC: distinct clinical entity

Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005–2014

M. Stenman a,*, G. Sinclair b, P. Paavola a, P. Wersäll c, U. Harmenberg c,1, M. Lindskog a,1

2018

No difference in local tx modality

Predictors of good outcomes

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Advanced RT techniques:
SBRT and
Profound hypofractionation
Stereotactic Ablative Body Radiotherapy

Stereotactic Body Radiotherapy (SBRT)

- Precise and focused delivery of small number of fractions of radiation in the ablative dose range to extracranial targets

Cone-based technique | LINAC technique | Cyberknife

Brain | Lungs | Head Neck

Beautiful technology treating small volumes in limited time
Stereotactic Ablative Body Radiotherapy

Stereotactic Body Radiotherapy (SBRT)
- Precise and focused delivery of small number of fractions of radiation in the ablative dose range to extracranial targets

Cone-based technique  LINAC technique  Cyberknife

Beautiful technology treating small volumes in limited time

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Volumetric arc therapy (VMAT)

Potential solution to minimise tx time and intrafx motion

- Tight margins ($\leq 5\text{mm}$) = smaller treatment volumes = ??? lower acute and late toxicity

- But tight margins demands high accuracy -> Intrafx motion becomes an issue

- VMAT reduces tx time significantly; ability to do real time tracking
Imaging to delineate small vol lesions

FDG and PSMA PET to target metastases and for surveillance of response post-SBRT

Siva et al., Journal of Medical Imaging and Radiation Oncology, 2017

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
Effective RT fractionation regimes

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Lesions (n)</th>
<th>Study design</th>
<th>Treated sites</th>
<th>Follow-up (months)</th>
<th>Dose and fractionation</th>
<th>Local control</th>
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<tbody>
<tr>
<td>Wersäll et al., 2005</td>
<td>50</td>
<td>162</td>
<td>Retrospective</td>
<td>Lung, lymph node, kidney, adrenal, liver, spleen, bone, thoracic wall, pancreas</td>
<td>37</td>
<td>4 times 8-10 Gy; 2-3 times 15 Gy</td>
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<td>Svedman et al., 2006</td>
<td>25</td>
<td>82</td>
<td>Prospective phase 2</td>
<td>Lung, lymph node, adrenal, thoracic wall, spleen</td>
<td>52</td>
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<td>Teh et al., 2007</td>
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<td>Bone, lung, lymph node, abdominal wall</td>
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<td>Zelefsky et al., 2012</td>
<td>58</td>
<td>105</td>
<td>Retrospective</td>
<td>Bone, lymph node</td>
<td>12</td>
<td>Once 18-24 Gy; 3 times 8-10 Gy; 5 times 4-12 Gy; 24-37 Gy in more than five fractions</td>
<td>44% at 3-5 yr</td>
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<td>39</td>
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<td>Bone, lymph node, lung, kidney, adrenal, liver, soft tissue</td>
<td>16</td>
<td>3 times 8-16 Gy; 10 times 4-5 Gy</td>
<td>91% at 2-0 yr</td>
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CR = crude rate. *Stipulates the uncertainty that the one grade 3 events in this series.

Table: Studies of oligometastasis from renal-cell carcinoma

Variety of extracranial sites

Meerleer et al., Lancet, 2014

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
## Effective RT fractionation regimes

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<td>44% at 3 yr</td>
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<td>Bone, lymph node, lung, kidney, adrenal, liver, soft tissue</td>
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<td>3 times 8-16 Gy; 10 times 4-5 Gy</td>
<td>91% at 2 yr</td>
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CR = crude rate. *Stipulates the uncertainty that the one grade 5 toxicity was due to stereotactic body radiotherapy in this study.

### Ablative regime

- **Schedule one:** 24 Gy in one fraction (BED 216 Gy, NID, 130 Gy)
- **Schedule two:** 32 Gy (16 Gy per fraction) in 1 week (BED 202 Gy, NID, 122 Gy)
- **Schedule three:** 36 Gy (12 Gy per fraction) in 1 week (BED 150 Gy, NID, 90 Gy; trial recruiting patients, EC 2013-1087)
- **Schedule four:** 35 Gy (7 Gy per fraction) in 2 weeks (BED 117 Gy, NID, 70 Gy)

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Meerleer et al., Lancet, 2014

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
Effective RT fractionation regimes

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CR = crude rate. *Stipulates the uncertainty that the one grade 5 toxicity was due to stereotactic body radiotherapy in this series.

Table: Studies of oligometastasis from renal-cell carcinoma with high-dose and high-dose-per-fraction radiotherapy

Excellent LC & minimal toxicities

Meerleer et al., Lancet, 2014
Understanding dose-fractionation

Biological Effective Dose

\[ BED = \text{Total Dose}(1 + \text{dose per } \#/\alpha/\beta) \]

- It is thought that “radioresistant” tumours like RCC have low \( \alpha/\beta \)
- \( \alpha/\beta = 1.5-2.0 \text{ Gy for tumour & 3.0 Gy for normal tissue} \)

**Conv - 50 Gy/25#**
- EQD2tumour = 100 Gy
- EQD2normal = 83.5 Gy

**SBRT**
- 24 Gy/2#
  - EQD2tumour = 168 Gy; EQD2normal = 120 Gy
- 30 Gy/3#
  - EQD2tumour = 180 Gy; EQD2normal = 130 Gy
- 40 Gy/5#
  - EQD2tumour = 200 Gy; EQD2normal = 147 Gy
Precision matching: targeting nodal mets

PET Contouring

RT plan

Daily matching – transverse

Coronal

Planning CT

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Precision matching: targeting spinal mets

RT contouring – Spine SRS consensus

International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery

IJORBP, 2012
Precision matching: targeting spinal mets

RT plan – Dose plan & constraints

Beam arrangements

Dose constraints
- Thecal sac – D0.03cc = 17 Gy
- Bowel – D0.03cc = 20 Gy
- Great vessel – D0.03cc <30 Gy

Dose distribution
Precision matching: targeting spinal mets

RT delivery techniques – VMAT (Arc) vs Multi-cone

**Pros and Cons**
- Single vs Multi-levels
- Speed of delivery – much faster with VMAT
- Dose for Single (24 Gy/2#) vs Multi-level (30-50 Gy/5#)
Future role of RT:
Novel therapeutics & Era of Immunotherapy
# Immunotherapy in mUC and mRCC

## Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma


<table>
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<tr>
<th>Target</th>
<th>Population</th>
<th>Response rate (n/N[%])</th>
<th>Median progression-free survival (months)</th>
<th>Median overall survival (months)</th>
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<tr>
<td>Atezolizumab</td>
<td>PD-L1, post-platinum metastatic urothelial carcinoma</td>
<td>45/310 (15%); 26/100 (26%)</td>
<td>2.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1, post-platinum metastatic urothelial carcinoma</td>
<td>7/44 (16%); 4/10 (40%)*</td>
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<tr>
<td>Pembrolizumab</td>
<td>PD-1, post-platinum metastatic urothelial carcinoma</td>
<td>8/29 (28%); 6/18 (33%)*</td>
<td>2.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4, muscle-invasive bladder cancer</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Gemcitabine plus cisplatin and ipilimumab</td>
<td>CTLA-4, metastatic urothelial carcinoma</td>
<td>23/36 (64%)</td>
<td>--</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Table 3: Results of clinical trials of checkpoint-inhibitor treatments in urothelial carcinoma published after 2010

## Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

**Checkmate-214, 2018**

- **12-Mo Overall Survival (95% CI)**: Nivolumab+Ipilimumab 80 (76–84) vs Sunitinib 72 (67–76).
- **18-Mo Overall Survival (95% CI)**: Nivolumab+Ipilimumab 75 (70–78) vs Sunitinib 60 (55–65).

- Hazard ratio for death, 0.63 (99.8% CI, 0.44–0.89), P<0.001

**Kamat, Lancet, 2016**

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigeisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

August 2009

November 2010

January 2011

April 2011

October 2011

December 2010

Recurrence of Unresectable Cancer

Ipilimumab

Induction — Maintenance — Radiation — Maintenance

Stable — Slow Progression — Response — Stable

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Yeo et al., Chin J Clin Oncol, 2017
Immunotx Combo with RT

Abscopal effect – case #2

Hepatocellular Carcinoma

Dramatic Local Control within 1 mo

Nivolumab → SBRT 30Gy/5# → Nivolumab

Interval reduction in previously stable para-tracheal LN
Immunotx Combo with RT

Abscopal effect – case #2

Dramatic Local Control within 1 mo

Hepatocellular Carcinoma

SBRT 30Gy in 5fr

Nivolumab

ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
Abscopal effect – case #2

Enhanced local response

Significantly increased rates of dramatic CR – defined as responses within 1 mo post-RT!!
Immunotx Combo with RT

**Questions**

- Dose/# regime-dependent
  (Lung study mostly SRT; whereas CNS primary SRS)
- Site-specific toxicities?
  (Brain vs lungs)
- Time to onset?

**References**

- Martin et al., JAMA Oncol, 2018
- Hwang et al., JAMA Oncol, 2018
- ESMO Preceptorship – Metastatic BC & RCC, 19 Sep 2018, Singapore
Summary

RCC

- “Radioresistant” no longer!!!
- Primary Role for RT remains palliation and local control
- However, LC may translate to improved survival in some oligometastatic patients
- Effective doses are typically large profound hypofractionation

UC

- Role for primary high intensity RT to the bladder remains undefined
- Chemo-sensitisation may be considered with concurrent gemcitabine (lower doses) to enhance RT efficacy

- Immunotherapy will be the systemic tx backbone for mRCC and mUC, hence there is a need to design novel RT-immuno combo to maximise local and systemic benefits.
Thank you!

Questions