Spatial Fractionation: Partial Tumor Irradiation

Dr. Tubin Slavisa

ASS. PROFESSOR AT ALBERT EINSTEIN COLLEGE OF MEDICINE NEW YORK
DIRECTOR OF CLINICAL RADIobiology, SCIENTIFIC CO-DIRECTOR
MEDAUSTRON CENTER FOR ION THERAPY AND RESEARCH

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548
Disclosures

I have no relevant financial relationships with ineligible companies to disclose.
„PATHY“ Approach

- PATHY: Partial Tumor irradiation targeting Hypoxic segment
- Novel, unconventional, immunomodulatory approach
- Designed for exploitation of the non-targeted effects of RT: bystander and abscopal.

- SBRT-PATHY\textsuperscript{2015} / \textit{Particle}-PATHY / \textit{CARBO}-PATHY\textsuperscript{2020}
PARTIAL TUMOR IRRADIATION USING CARBON IONS

- **CARBO-PATHY** = CARBON ion-based PARTial Tumor irradiation targeting HYpoxic segment
- **IMMUNOGENEICITY** = CARBON ions + highly heterogeneous dose + HYPOXIC target + IMMUNE-SPARING.
PATHY: Partial Tumor irradiation targeting Hypoxic tumor segment

- 3 key-components of PATHY:
  1.) PARTIAL TUMOR IRRADIATION TARGETING HYPOXIC SEGMENT
  2.) SPARING OF PERITUMORAL IMMUNE MICROENVIRONMENT (NEW OAR)
  3.) TIME-SYNCHRONIZED IMMUNE-GUIDED TUMOR IRRADIATION
TARGET-VOLUME: HYPOXIC TUMOR SEGMENT

1. Tumor hypoxia is a potent immunosuppressor (abolished IFN-1β response, enhances expression of immunosuppressive proteins),
2. Hypoxic tumor cells stronger abscopal inductor.

PRECLINICAL RESULTS ON BYSTANDER/ABSCOPAL EFFECT-INDUCTION:

10Gy SINGLE DOSE irradiation of the HYPOXIC (vs. normoxic) tumor = stronger bystander effect!

TUMOR GROWTH after induction of abscopal effect with 10Gy x 1 to the hypoxic tumor
INDICATIONS

unresectable, recurrent bulky tumors unsuitable for conventional RT-CHT/RE-IRRADIATION
Prescription of heterogeneous dose(-gradients):

INITIAL: 10-12Gy x 1 to 60-70% (2015)

ESCALATED: 15Gy x 3 to 60-70% (2020)

DOSE: HIGH, HETEROGENEOUS, GRADIENTs

E-mail: slavisa.tubin@medaustron.at
CRP, LDH, IL-2, IFNg and Lymphocyte/Monocyte analyzed for levels and cyclical fluctuations to determine each patient’s idiosyncratic immune cycle’s periodicity and then each patient’s time-position of initiation of treatment and response to therapy.
Median follow-up: 12 months (4–22).

Optimally synchronized SBRT-PATHY with the favourable immune cycle period was associated with improved clinical outcomes (three complete responses plus significant abscopal effects in 3 patients).

Time-synchronized immune-guided SBRT partial bulky tumor irradiation targeting hypoxic segment while sparing the peritumoral immune microenvironment

E-Mail: slavisa.tubin@medaustron.at
Osvaldo Tubin, Antonio Carlino, Giovanna Martino, Joanna Gora, Markus Stok and Eugen Hug

Table 1. Treatment characteristics of the selected studies.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Retrospective</td>
<td>Retrospective phase II</td>
<td>Retrospective</td>
<td>Retrospective phase III</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Number of patients under SBRT-PATHY</td>
<td>7</td>
<td>20</td>
<td>8</td>
<td>23</td>
<td>3</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Median follow up (months)</td>
<td>6 (2–9)</td>
<td>13 (4–27)</td>
<td>7 (1–15)</td>
<td>9.4 (4–20)</td>
<td>5.3 (3–7)</td>
<td>11.8 (4–22)</td>
<td>9 (4–12)</td>
</tr>
<tr>
<td>Local control (bystander effect)</td>
<td>100%</td>
<td>95%</td>
<td>83%</td>
<td>96%</td>
<td>67%</td>
<td>75%</td>
<td>73%</td>
</tr>
<tr>
<td>Abscopal response</td>
<td>28.6%</td>
<td>45%</td>
<td>Not evaluable</td>
<td>52%</td>
<td>Not evaluable</td>
<td>50%</td>
<td>47%</td>
</tr>
<tr>
<td>Symptom relief</td>
<td>100%</td>
<td>80%</td>
<td>100%</td>
<td>96%</td>
<td>67%</td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>Treated symptoms</td>
<td>Dyspnea, pain</td>
<td>Dyspnea, pain, cough, hemoptysis</td>
<td>Pain, bleeding</td>
<td>Dyspnea, pain, cough, Dyspnea, pain, cough</td>
<td>Pain, Dysphagia</td>
<td>Dyspnea, pain, cough, Dyspnea, pain, cough, hemoptysis, edema-extremities, dysphonia</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>none</td>
<td>Fattigue GI (15%)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>Fattigue GI (20%)</td>
</tr>
<tr>
<td>Hematological toxicity/leucopenia</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Median total dose/dose-fraction (Gy)</td>
<td>10/10</td>
<td>10-30/10</td>
<td>10/10</td>
<td>10-30/10</td>
<td>36/12</td>
<td>30/10</td>
<td>30/10</td>
</tr>
</tbody>
</table>
RADIOBIOLOGICAL EFFECTS OF PATHY
Large spectrum of malignancies: lung, H&N, kidney, liver, pancreas, rectum, brain, prostate, adrenal etc.
PATHY: safety

The only side effects observed were flu-like symptoms.

Table 1. Treatment characteristics of the selected studies.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Retrospective</td>
<td>Retrospective phase II</td>
<td>Retrospective case series (re-irradiation)</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Toxicity</td>
<td>none</td>
<td>Fatigue G1 (15%)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>Fatigue G1 (20%)</td>
</tr>
<tr>
<td>Hematological toxicity/leucopenia</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>
METASTATIC MELANOMA

Progressive under immunotherapy

DOSE: 10Gy x 1 to 70%

Disease free till death (2 years)
THREE FRACTION

HCC

Progressive under immunotherapy

DOSE: 10Gy x 3

BEFORE PATHY

1 MONTH AFTER PATHY

70% volume regression

PATHY: immunogenic effects

BYSTANDER EFFECT

ABSCOPAL EFFECT

E-Mail: slavisa.tubin@medauston.at
BEFORE

AFTER

90% volume regression

HOT

DESMOID

Progressive under IMMUNO Tx

DOSE: 10Gy x 3

BYSTANDER EFFECT

ABSCOPAL EFFECT

E-Mail: slavisa.tubin@medaustron.at
BYSTANDER

ABSCOPAL

12 cm large sternum bulky metastasis of the primary breast cancer: before SBRT-PATHY, Axillary nodal metastases unirradiated.

BREAST (cM1)

Progressive under CHT

DOSE: 10Gy x 3

NED / clinical complete response

Unirradiated primary breast cancer: before (up) and after (down) SBRT-PATHY; complete response due to the abscopal effect;

E-Mail: slavisa.tubin@medauston.at
SYNCHRONOUS ABSCOPAL

BEFORE PATHY

RECTUM

DOSE: 10Gy x 3

2 MONTH AFTER PATHY

Synchronous colon cancer

70% volume regression

E-Mail: slavisa.tubin@medauston.at
RESPONSE DYNAMIC: AFTER 2 WEEKS!!

LYMPH NODE METASTASIS OF THE SQUAMOUS CELL H&N

DOSE: 10Gy x 1 to 70%

50% volume regression

FIGURE 1. RADIATION OF THE BYSTANDER EFFECT: A) A voluminous left neck lymph nodal metastasis of the squamous cell carcinoma of the right ear; B) Definition of the hypoxic bystander tumor volume (BTV) - smaller pink contour; GTV - bigger pink contour; bystander signals (blue pellets red arrows) released by the irradiated GTV; C) An induction of the bystander effect with a high-dose partial irradiation of the GTV (red contour) by targeting the BTV (green contour); D) A reduction of 50% in the treated lesion only 2 weeks later.
DEDIFFERENTIATED LIPOSARCOMA

Before CARBO-PATHY

5 months after partial tumor irradiation

AFTER 5 MONTHS

50% volume regression
ADENOID-CYSTIC CARCINOMA OF LUNG

Before CARBO-PATHY

1 month after partial tumor irradiation

80% volume regression

RADIO-RESISTANT TUMORS

DOSE: 15Gy x 3

E-Mail: slavisa.tubin@medautstron.at
G2 LIPOSARCOMA

dose: 15Gy x 3

60% volume regression
COMPLETE RESPONSE

Before SBRT-PATHY

PRIMARY ADC OF THE LUNG

7 months after partial tumor irradiation
10Gy x 1 to the 70%

slavisa.tubin@medaustron.at
LONG- and SHORT-lasting RESPONSES

SECONDARY GERMINOMA, 10Gy x 3

SCC FLOOR OF MOUTH, 15Gy x 3

DESMOID
10Gy x 3

2 months

6 months

18 months

E-Mail: slavisa.tubin@medaustron.at
NEOADJUVANT POTENTIAL by UNRESECTABLE RADIORESISTANT BULKY TUMORS

DEDIFFERENTIATED LIPOSARCOMA

G2 LIPOSARCOMA

ADENOID-CYSTIC
Prediction of abscopality

Predictive by the local response: ≥ 50%

E-Mail: slavisa.tubin@medauston.at
SURVIVAL UNDER PATHY

LIFE EXPECTANCY
• Palliative Prognostic Index: <2 months!

PATHY (only 1 course)

OVERALL SURVIVAL
8 months

E-mail: slavisa.tubin@medunigraz.at
**Mechanisms behind the Pathy Non-Targeted Effects**

**Immunohistochemistry**

- **Immunohistochemistry** was performed using antibodies for *apoptosis-inducing factor* (AIF), CD3, CD4, CD8, CD20, CD56, CD14, CD15, and S100 protein to explore for the activation and modifications within the tumor microenvironment.

- **Gene analysis** focused on the expression of *cell death and immune activation-related genes* in the necrotic tumor, PIM and abscopal sites. Specific regions were identified from H&E stained sections cut in parallel and dissected from the slides to isolate RNA. RNA was reverse transcribed and qPCRs were run on a Biorad CFX 96 Real-Time System.

AIF was massively upregulated in the partially irradiated bulky, but also at abscopal tumor sites.
Abundant infiltration of the CD20+ B-lymphocytes, CD3+/CD8+ T-lymphocytes was observed, indicating a possible anti-tumor-directed-activation of the immune system!

- The same signs of immune system activation at abscopal site were clearly absent.
Despite absent immune infiltration, those apoptotic abscopal sites showed a strong expression of the cell death-inducing cytokines! For AIF, IL-6, and TNFA, abscopal sites had higher expression levels compared to the partially irradiated tumors, suggesting an abundance of potentially cell death-inducing signals not only in the partially irradiated tumors but even more so in non-irradiated abscopal sites.
Conclusions

• RT has great immunogenic potential, can brake tolerance, convert cold into hot environments!

• PARTIAL T Rx resulted in effective, safe and well tolerated treatment.

• Improvement in symptoms and quality of life without associated treatment related toxicity.

• PATHY resulted in varying degrees of tumor downsizing (neoadjuvant effect!).

• Optimum patient selection and definition of most suitable disease characteristics are currently explored in an ongoing, prospective study.

1.) Particle-based Partial Tumor Irradiation of Unresectable Bulky Tumors (PARTICLE-PATHY)

ClinicalTrials.gov

MedAustron

KABEG Klinikum Klagenfurt

ClinicalTrials.gov

Hypothesis-generating study on the mechanisms behind radiation-hypoxia-induced abscopal response

Recruitment Status: Recruiting

2.) SBRT-based PArtial Tumor Irradiation of HYpoxic Segment (SBRT-PATHY)

ClinicalTrials.gov

Recruitment Status: Recruiting

E-Mail: slavisa.tubin@medaustron.at