IX Congresso Internacional de Uro-Oncologia

IV SIMPÓSIO MULTIPROFISSIONAL DE URO-ONCOLOGIA

1 a 3 de Março de 2018

SHERATON SÃO PAULO WTC HOTEL
PÓS ASCO GU 2018

Testicular Câncer

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1- Keynote Letter: Manejo de Câncer de Testículo estadio II (A) com marcador tumoral negativo

2- General Session: Manejo de massas residuais pós quimioterapia
   - Abstract 546- Serum miRNA to predict post-chemotherapy viable disease in testicular non-seminomatous germ cell tumor patients.

3- Rapid-Fire Abstract Session:
   - Abstract 550- Sentinel node biopsy in clinical stage I testicular cancer;
   - Abstract 549- Long-term sexual functioning in germ-cell tumor survivors;
   - Abstract 551- Impact of medicaid expansion on diagnosis and management of patients with testicular cancer

4- Poster:
   - Abstract 548- Collateral damage: Molecular aging and p16INK4a senescence protein in testicular cancer survivors treated with chemotherapy.
   - Abstract 564- Effect of number of computed tomography (CT) scans during follow-up (FUP) of patients with clinical stage I (CSI) seminoma: A trial-level meta-analysis.
   - Abstract 556 -Diagnostic radiation and testicular germ cell tumor risk.

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Serum miRNA to predict post-chemotherapy viable disease in testicular nonseminomatous germ cell tumor patients

Ricardo Leão MD
Dept. of Surgical Oncology, Princess Margaret Cancer Centre
Toronto, Canada

PIs: Robert J Hamilton MD MPH and Leendert Looijenga PhD

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Presented at 2018 Genitourinary Cancers Symposium | #GU18
Background

- **Post Chemotherapy Retroperitoneal Lymph Node Dissection (pcRPLND)** is part of multimodal treatment for patients with advanced nonseminoma testicular germ cell tumors
- Currently indicated in patients with *normalized* or *plateaued* serum tumor markers with residual disease (> 1 cm)
- **Rationale** to remove residual masses:
  - Teratoma (40-45%),
  - Viable chemorefractory germ cell tumor elements (10-15%)


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The problem...

Approximately 50% of patients are submitted to unnecessary surgery

- Tumor Markers (AFP, LDH, HCG)
- Imaging
- Predictive Models

Post-chemotherapy Radiographic Histology

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miRNAs in Testicular Cancer

Diagnostic Properties

Prognostic Properties


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Hypothesis

*Serum miRNAs are predictive markers for viable disease post-chemotherapy*
Patients and Methods

NSGCT patients submitted to orchiectomy, chemotherapy and pcRPLND

Cohort A
n=39

Cohort B
n=43

Pre Chemotherapy

n=39

Post Chemotherapy
Pre. RPLND

n=82

Post RPLND

ampTSmiR Test

miR-371a-3p

miR-373-3p

miR-367-3p


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Patients and Methods

Post Chemotherapy Lesion Histology

Cohort A and B

n=82

<table>
<thead>
<tr>
<th>Necrosis/Fibrosis</th>
<th>36 (43.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratoma</td>
<td>34 (41.5%)</td>
</tr>
<tr>
<td>Viable GCT</td>
<td>12 (14.6%)</td>
</tr>
</tbody>
</table>

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Results

Classical tumor markers do not predict post-chemotherapy residual masses histology

- **AFP**
- **HCG**
- **LDH**

(a) AFP:
- Fibrosis/Necrosis
- Teratoma
- Viable

(b) HCG:
- Fibrosis/Necrosis
- Teratoma
- Viable GCT

(c) LDH:
- Fibrosis/Necrosis
- Teratoma
- Viable GCT

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Results

Pre-chemotherapy serum miRNA levels are associated with clinical stage

(Cohort A. n=39. A. *, p =0.046; B. **, p =0.003; C.*, p =0.038)

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Results

Serum miRNA levels are associated with treatment response

miR-371a-3p

miR-373a-3p

miR-367-3p

(Cohort A. n=39. A. miR-371, ****, p <0.0001, ***, p =0.0006; B. miR-373, **, p =0.0025; C. miR-367, **** p <0.0001, . **, p =0.005 .).
Results

Serum miRNA levels are higher in the presence of viable GCT post-chemotherapy

- miR-371a-3p
- miR-373a-3p
- miR-367-3p

(Cohort A. n=39. A. ***, p=0.0002, **, p=0.004; B. *, p=0.037; C. **, p=0.011, *, p=0.024)

Pre-published at 2018 Genitourinary Cancers Symposium | #GU18

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Results

Serum miRNA levels are higher in the presence of viable GCT post-chemotherapy

miR-371a-3p

miR-373a-3p

miR-367-3p

(Cohort A. n=39. A. ***, p=0.0002, ** p=0.004; B. * p=0.037; C. **, p=0.011, * p=0.024)

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Results

Serum miRNA levels are higher in the presence of viable GCT post-chemotherapy

miR-371a-3p

miR-373a-3p

miR-367-3p

(Cohort A. n=82. A. ***; p=0.002; B.*, p=0.032)

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Results

Serum miRNA accurately predict presence of viable GCT post-chemotherapy

Viable GCT vs. Fibrosis/Necrosis + Teratoma (n=82, post-chemotherapy)

- miR-371a-3p/miR-373-3p (AUC 0.885, 95% CI 0.79-0.98)
- miR-371a-3p/miR-373-3p/miR-367 (AUC 0.889, 95% CI 0.79-0.99)
- miR-371a-3p (AUC 0.874, 95% CI 0.77-0.97)
- miR-371a-3p/miR-367 (AUC 0.873, 95% CI 0.78-0.98)
- miR-373-3p (AUC 0.738, 95% CI 0.59-0.88)
- miR-367 (AUC 0.707, 95% CI 0.54-0.87)

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Results

Serum miR-371a-3p levels post-chemotherapy might support treatment decision in patients with residual retroperitoneal masses ≤ 3 cm

miR-371a-3p cut-off level 2.0 (Sensitivity 100%, Specificity 54%; NPV 100%, p=0.02)

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Conclusions/Take-Home Points

- Serum miRNA are associated with *clinical stage and treatment response*
- miR-371a-3p, as a single serum marker, accurately *predicts viable disease post-chemotherapy*
- In a sub-group of patients with retroperitoneal lesions measuring ≤ 3 cm, *miR-371a-3p profile might support treatment decision*
- *Promising but future studies are needed* to confirm our findings

Presented by Ricardo Leão et al.

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Limitations

- *Small cohort* of patients
- *Heterogeneous* population
- *Inability to distinguish teratoma* from necrosis & fibrosis
- Difficult to establish *correlation* with other studies using serum miRNAs (different assays and different population of testicular cancer patients)
- *Multi-institutional studies* with *standard miRNA quantification* assays are *needed* to establish miRNAs as clinical biomarkers

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Presented By Ricardo Leao at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care
Sentinel Node Biopsy in Clinical Stage I Testicular Cancer

Joost Blok, MD
Physician-researcher / PhD Candidate

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Testicular tumor
850 / year in NL (8850 in USA)

Clinical Stage I
Orchiectomy & active surveillance

No relapse
80%
Seminoma
20%
Non-seminoma
30%
Occult metastatic disease
Relapse

25%
Stage II or higher

75%

70%
No relapse

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Sentinel Lymph Node Biopsy

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1. Funicular block

2. Intratesticular injection radiopharmaceutical

3. Lymphoscintigraphy SPECT/CT

4. Laparoscopic resection SN

5. Radical orchiectomy

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Presented By Joost Blok at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care
Lymphoscintigraphy & SPECT/CT

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Results
27 patients → 2 pts no SN visualization

25 patients
SN biopsy

→ 2 pts no TGCT

23 pts TGCT

16 pts seminoma
7 pts non-seminoma

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27 patients

25 patients
SN biopsy

23 pts TGCT

16 pts seminoma

7 pts non-seminoma

2 pts no SN visualization

2 pts no TGCT

20 pts SN negative

No complications

3 pts (13%) SN positive
(2 seminoma, 1 non-seminoma)

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Follow-up results
3 patients SN positive

Adjuvant chemotherapy

BEP x4
CEB x4
Carbo x2

Median follow-up 63.9 mos. (29.0 – 143.4)

No relapse

20 patients SN negative

No relapse
Take-home messages

• SN makes early identification of patients with occult metastatic disease possible

• Negative SN $\rightarrow$ no relapse (n=20)
Adjusted treatment?

- SN negative: less intensive follow-up
- SN positive: less toxic treatment, at an early stage
However...

- Additional invasive procedure
  - Additional risk of complications

- ‘Unnecessary’ in some patients
SENATOR Study

- SEntinal lymph Nodde procedure in testicular germ cell TumOur
- 76 patients
- Netherlands Cancer Institute and University Medical Center Utrecht
- Aim: investigate whether SN negative patients will experience relapse
Long-term sexual functioning in germ-cell tumor survivors


Faculty of Medicine, Comenius University in Bratislava
National Cancer Institute of Slovakia

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Background

- Germ-cell tumors (GCTs) – curative Tx
- Late toxic treatment sequelae \(^1,^2\)
- Issues in quality of life
- Self reported outcomes – important in cancer care \(^3\)

\(^1\) Haugnes HS et al. J Clin Oncol 2012, 30: 3752–3763
\(^3\) Basch EM et al. J Clin Oncol, 2017, 35 (suppl. abstr: LBA2)
Study design and participants

- Prospective study
- GCT survivors > 5 years after Tx (n=170)
- Median follow up – 10 yrs
- PROMIS modified sexual function questionnaire

Study groups

- CT (n = 141)
- XRT (n = 12)
- CT+XRT (n = 9)
- Orchiectomy (n = 17)
- Total = 170

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Education, job, marital status and fatherhood

- No differences between study groups
- All $P > 0.05$
Results

Ability to achieve an erection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Score (range 0-5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORCH</td>
<td>4.47</td>
<td>0.20</td>
</tr>
<tr>
<td>CT</td>
<td>3.87</td>
<td>0.12</td>
</tr>
<tr>
<td>XRT</td>
<td>3.5</td>
<td>0.05</td>
</tr>
<tr>
<td>XRT+CT</td>
<td>2.89</td>
<td>0.18</td>
</tr>
<tr>
<td>ANY TX</td>
<td>3.84</td>
<td></td>
</tr>
</tbody>
</table>

Ability to maintain an erection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Score (range 0-5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAINTAIN ERECTION (SCORE RANGE 0-5)</td>
<td>4.47</td>
<td>0.04</td>
</tr>
<tr>
<td>ORCH</td>
<td>3.67</td>
<td></td>
</tr>
</tbody>
</table>

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### Results

#### Ability to achieve an orgasm

<table>
<thead>
<tr>
<th>Achieve Orgasm (Score Range 0-5)</th>
<th>ORCH</th>
<th>Pt &gt; 400 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>4.64</td>
<td>3.92</td>
</tr>
</tbody>
</table>

#### Disappointed by sex life

<table>
<thead>
<tr>
<th>Disappointed by Sex Life</th>
<th>ORCH</th>
<th>CT</th>
<th>XRT</th>
<th>XRT+CT</th>
<th>Any Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.23</td>
<td>0.06</td>
<td>0.003</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Score (range 1-4)</td>
<td>1.35</td>
<td>1.67</td>
<td>2.08</td>
<td>2.56</td>
<td>1.7</td>
</tr>
</tbody>
</table>

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Results

Anxiety from a sexual relationship

<table>
<thead>
<tr>
<th></th>
<th>ORCH</th>
<th>CT</th>
<th>XRT</th>
<th>XRT+CT</th>
<th>ANY TX</th>
</tr>
</thead>
<tbody>
<tr>
<td>score</td>
<td>1.41</td>
<td>1.4</td>
<td>1.83</td>
<td>1.56</td>
<td>1.43</td>
</tr>
<tr>
<td>P value</td>
<td>0.69</td>
<td>0.37</td>
<td>0.74</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

Desire to be sexually active

<table>
<thead>
<tr>
<th></th>
<th>ORCH</th>
<th>CT</th>
<th>XRT</th>
<th>XRT+CT</th>
<th>ANY TX</th>
</tr>
</thead>
<tbody>
<tr>
<td>score</td>
<td>2.88</td>
<td>2.86</td>
<td>3.08</td>
<td>3.67</td>
<td>2.87</td>
</tr>
<tr>
<td>P value</td>
<td>0.90</td>
<td>0.71</td>
<td>0.05</td>
<td>0.94</td>
<td></td>
</tr>
</tbody>
</table>

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Results

- Serious to severe impairment:
- 10 – 33 % of all survivors
<table>
<thead>
<tr>
<th>Variable</th>
<th>Testosterone (ng/mL)</th>
<th>N</th>
<th>Mean</th>
<th>SEM</th>
<th>Median</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual desire</td>
<td>&lt; 300</td>
<td>102</td>
<td>3.2</td>
<td>0.08</td>
<td>3</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>22</td>
<td>2.9</td>
<td>0.19</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Attempts to initiate intercourse</td>
<td>&lt; 300</td>
<td>102</td>
<td>2.4</td>
<td>0.15</td>
<td>2</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>22</td>
<td>2.1</td>
<td>0.34</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Achieve erection</td>
<td>&lt; 300</td>
<td>102</td>
<td>4.1</td>
<td>0.17</td>
<td>5</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>22</td>
<td>3.5</td>
<td>0.36</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Maintain erection</td>
<td>&lt; 300</td>
<td>102</td>
<td>4.0</td>
<td>0.16</td>
<td>5</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>22</td>
<td>3.0</td>
<td>0.35</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Achieve orgasm</td>
<td>&lt; 300</td>
<td>101</td>
<td>4.3</td>
<td>0.14</td>
<td>5</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>21</td>
<td>4</td>
<td>0.31</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Disappointed with quality of sex life</td>
<td>&lt; 300</td>
<td>101</td>
<td>1.7</td>
<td>0.09</td>
<td>1</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>21</td>
<td>1.6</td>
<td>0.20</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Anxiety from sexual relationships</td>
<td>&lt; 300</td>
<td>101</td>
<td>1.4</td>
<td>0.08</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>&gt; 300</td>
<td>21</td>
<td>1.8</td>
<td>0.18</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Limitations

- Small numbers in some groups
- XRT and XRT+CT: need validation in a large cohort
Conclusions

- Sexual functioning - serious issue in GCT srvs
- The highest risk - XRT
  - XRT+CT
  - cumulative Pt > 400 mg/m²
- Sexual impairment – independent of low testosterone levels
CONCLUSÃO

Estudos geradores de hipóteses, nenhum “practice changing”:

1- Manejo de massas residuais pós quimioterapia
   ❖ Abstract 546- Serum miRNA to predict post-chemotherapy viable disease in testicular non-seminomatous germ cell tumor patients.

2- Biópsia de LN sentinela como ferramenta de seleção de pacientes ECI q vão receber tratamento adjuvante ou definir melhor o seguimento desses pacientes, inclusive sobre a frequência de exames de imagem que vão realizar
   ❖ Abstract 550- Sentinel node biopsy in clinical stage I testicular cancer;

3- Toxicidade a longo prazo – importância da disfunção sexual na qualidade de vida de pacientes sobreviventes ao pacientes sobreviventes ao tratamento de câncer de testículo
   ❖ Abstract 549- Long-term sexual functioning in germ-cell tumor survivors;

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OBRIGADA!