Image-guided radiotherapy (IGRT) in oligometastatic recurrent prostate cancer

Piet Dirix MD, PhD
Radiation Oncology
Iridium Cancer Network
www.iridiumkankernetwerk.be
Intensity-modulated radiotherapy (IMRT)
Image-guided radiotherapie (IGRT)

IGRT = making sure that treatment is delivered as planned

On-board Imaging (OBI)

- MV X-ray tube
- kV On-Board Image Detector
- EPID MV Imager
- kV X-ray tube
kV-MV “matching” on bony anatomy
kV-MV “matching” on fiducial (= gold) markers
CB-CT “matching” on soft tissue
Future prospect: MR “matching” on MR-Linac

ViewRay (MRIdian)  

University of Alberta

UMC Utrecht (Elekta-Philips)  

Australian MR-Linac program
### MR-guided RT allows for true soft tissue matching

<table>
<thead>
<tr>
<th>Linac – Cone-beam CT</th>
<th>MRIedian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>✗</strong> Eliminate X-ray radiation</td>
<td>✔</td>
</tr>
<tr>
<td><strong>✗</strong> Don’t use registration markers</td>
<td>✔</td>
</tr>
<tr>
<td><strong>✗</strong> Differentiate between soft tissues and tumor</td>
<td>✔</td>
</tr>
<tr>
<td><strong>✗</strong> Ability to locate, target and track the tumor directly</td>
<td>✔</td>
</tr>
</tbody>
</table>

Ultimate combination of IMRT and IGRT: SABR

1. GTV delineated on MRI and/or PET.
2. No or limited CTV.
3. PTV margins < 0.5 cm.
4. Good quality daily IGRT is essential.
5. Extremely hypofractionated.

SABR = stereotactic ablative body radiotherapy
Contemporary treatment of prostate cancer

Primary treatment:
Surgery +/- RT
RT +/- ADT

PSA failure
Median 5 years after RT
Median 10 years after RP

M1 disease
11 (5 – 29) months

mCRPC disease
TAX 327
TROPIC
COU-AA-301
COU-AA-302
AFFIRM
PREVAIL
IMPACT
ALSYMPCA

References:
## Treatment of mCRPC

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Treatment</th>
<th>Control</th>
<th>Median OS benefit</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 327</td>
<td>1006</td>
<td>Docetaxel + prednisone</td>
<td>Mitoxantrone + prednisone</td>
<td>2.9 months</td>
<td>0.004</td>
</tr>
<tr>
<td>TROPIC</td>
<td>755</td>
<td>Cabazitaxel + prednisone</td>
<td>Mitoxantrone + prednisone</td>
<td>2.4 months</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>1195</td>
<td>Abiraterone + prednisone AFTER Cx</td>
<td>Placebo + prednisone AFTER Cx</td>
<td>3.9 months</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>1088</td>
<td>Abiraterone + prednisone BEFORE Cx</td>
<td>Placebo + prednisone BEFORE Cx</td>
<td>4.4 months</td>
<td>0.01</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>1199</td>
<td>Enzalutamide AFTER Cx</td>
<td>Placebo AFTER Cx</td>
<td>4.8 months</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>1717</td>
<td>Enzalutamide BEFORE Cx</td>
<td>Placebo BEFORE Cx</td>
<td>2.2 months</td>
<td>NS</td>
</tr>
<tr>
<td>IMPACT</td>
<td>512</td>
<td>Sipuleucel-T</td>
<td>Placebo</td>
<td>4.1 months</td>
<td>0.03</td>
</tr>
<tr>
<td>ALSYMPCA</td>
<td>922</td>
<td>Radium-223</td>
<td>Placebo</td>
<td>3.6 months</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
### Table 3. Treatment Costs in Patients With CRPC for 30-Day Period (oral drugs) or One Infusion/Cycle (parenteral drugs)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Approval Date</th>
<th>Large Group Insurance Rate ($)*</th>
<th>Commercial Rate ($)*</th>
<th>Medicare Rate ($)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>2011</td>
<td>5,171.90</td>
<td></td>
<td>6,409.11</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>1995</td>
<td>Generic, 82; brand, 520</td>
<td>Generic, 28; brand, 527</td>
<td></td>
</tr>
<tr>
<td>Cabazitaxel†</td>
<td>2010</td>
<td>11,233.78</td>
<td></td>
<td>12,806.06</td>
</tr>
<tr>
<td>Degarelix</td>
<td>2008</td>
<td>445.53</td>
<td></td>
<td>536.75</td>
</tr>
<tr>
<td>Docetaxel†</td>
<td>1999</td>
<td>Brand (pregeneric), 3,006.19</td>
<td>Generic, 681.67</td>
<td></td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>2012</td>
<td>†</td>
<td></td>
<td>7,906.34</td>
</tr>
<tr>
<td>Flutamide</td>
<td>1989</td>
<td>79.65</td>
<td></td>
<td>125.80</td>
</tr>
<tr>
<td>Goserelin acetate</td>
<td>1995</td>
<td>596.00</td>
<td></td>
<td>210.32</td>
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<tr>
<td>Ketoconazole</td>
<td>1999</td>
<td>66.52</td>
<td></td>
<td>19.22</td>
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<tr>
<td>Leuprolide acetate</td>
<td>1998</td>
<td>356.00</td>
<td></td>
<td>202.84</td>
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<tr>
<td>Mitoxantrone†</td>
<td>1987</td>
<td>615.63</td>
<td></td>
<td>203.96</td>
</tr>
<tr>
<td>Nilutamide</td>
<td>1996</td>
<td>464.13</td>
<td></td>
<td>4,201.38</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1974</td>
<td>3.75</td>
<td></td>
<td>6.50</td>
</tr>
<tr>
<td>Radium-223</td>
<td>2013</td>
<td>12,455.00 †</td>
<td></td>
<td>12,455.00 †</td>
</tr>
<tr>
<td>Sipuleucel-T§</td>
<td>2010</td>
<td>40,670.42</td>
<td></td>
<td>34,672.58</td>
</tr>
</tbody>
</table>

*Prices in U.S. dollars.
†Prices for generic and brand-name versions.
‡Prices vary by location.
§Data not available.

Individualized treatment: local relapse

Primary treatment:
Surgery +/- RT
RT +/- ADT

PSA failure
Median 5 years after RT
Median 10 years after RP

M1 disease
11 (5 – 29) months

mCRPC disease

Post ADT R/

References:
Innovative imaging to detect local relapse

Systematic review of PET & MRI for local recurrence

<table>
<thead>
<tr>
<th>Index test (n_{se}/n_{sp})</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>T2w (6/6)</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>T2w and DCE (11/10)</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>T2w and DWI (7/6)</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>MRS (3/2)</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td>MRS and DCE (4/4)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>mpMRI (3/4)</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>[^{11}C]Acetate (3/2)</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>[^{11}C]Choline (8/8)</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>[^{18}F]Choline (6/6)</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>[^{18}F]FECH (2/2)</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>
Patients with local recurrence need dose-escalation

Image-guided, dose-escalated salvage IMRT (1)

35x 2.2/2.0/1.6 Gy to local recurrence/prostate bed/pelvis.
Results: biochemical disease-free survival (bDFS).
Individualized treatment: regional relapse

Primary treatment:
Surgery +/- RT
RT +/- ADT

PSA failure
Median 5 years after RT
Median 10 years after RP

M1 disease
11 (5 – 29) months

mCRPC disease
Post ADT R/

References:

TAX 327
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Towards individualized treatment: nodal staging

Prostate cancer: small metastases in small lymph nodes.

Towards individualized treatment: $^{68}\text{Ga-PSMA PET-CT}$

A new (and very sexy) kid on the block.

PSMA-PET/CT has fueled oligometastatic disease
PET imaging only shows the tip of the iceberg

UZ Leuven data (courtesy of S. Joniau):

- 59.4% (19/32) correct prediction
- 40.6% (13/32) false positive
- 82.9% (92/111) false negative

NEED FOR EXTENDED LND TEMPLATES !!!

Table 2 – Percent sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of positron emission tomography/computed tomography in the detection of lymph node metastases

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient analysis (n = 56)</td>
<td>-</td>
<td>-</td>
<td>85.7% (48/56)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Node analysis (n = 1149)</td>
<td>39.7% (112/282)</td>
<td>95.8% (831/867)</td>
<td>75.7% (112/148)</td>
<td>83.0% (831/1001)</td>
<td>82.1% (943/1149)</td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value.

A positive PET-CT correctly predicts the presence of LN+ in the majority of patients with biochemical failure after radical prostatectomy but does not allow for localization of all metastatic LN and therefore is not adequately accurate for the precise estimation of extent of nodal recurrence in these patients.
Subsequent relapses after SBRT are again nodal and oligometastatic
Image-guided, dose-escalated salvage RT

25x 2.64/2.0 Gy to LN+/pelvis after earlier salvage prostate bed RT.
Individualized treatment: bony oligometastases

Primary treatment:
Surgery +/- RT
RT +/- ADT

PSA failure
Median 5 years after RT²
Median 10 years after RP³

M1 disease
11 (5 – 29) months⁴,⁵

mCRPC disease

ADT

Post ADT R/

References:

Median 5 years after RT:
27 (14 – 51) months¹

Median 10 years after RP:
1 (14 – 51) months¹
The “spectrum” paradigm

EDITORIAL

Oligometastases

“This thesis argues that cancer comprises a biologic SPECTRUM extending from a disease that remains localized to one that is systemic when first detectable but with many intermediate states.

Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread. Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic.

What is important in oligometastases is the recognition that it is not just a stochastic oddity, but rather that it is based on a state of LIMITED METASTATIC CAPACITY and is a characteristic of many tumors during their clinical evolution.

An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients should be amenable to a CURATIVE therapeutic strategy.”

Metastasis occurs late in the evolution of genetic change.

The capacity for metastatic spread is likely an epiphenomenon of the genetic instability of the primary tumor. There are primary tumor cells that have limited capability in one or more of the necessary biological requirements for metastasis: the origin of oligoM+. 

Oligometastases in prostate cancer

Metastatic potential

Loco-regional treatment

Tumor load is an important prognostic factor

Crucial cut-off: ≤ 5 metastatic lesions.
Does a true oligometastatic phenotype exist?

**Gene signature**

- [Image](#)

**CTC/DTC**

- [Image](#)

**microRNA expression**

- [Image](#)

References:
Innovative imaging techniques.

Bone scan will detect M+ in patients with a high PSA level (> 10 µg/L).

WB-MRI & PSMA-PET/CT can detect smaller lesions in asymptomatic patients with low, but rising, PSA (even < 5 µg/L).

61-year old with rising PSA after RP for pT3aN0 PrCa, Gleason 10. Current PSA: 0,27 µg/L.

Bone scan negative, solitary lesion in D2 on whole-body MRI & PSMA-PET/CT.

Start hormonal treatment or “salvage” SABR in effort to postpone ADT?
Stereotactic ablative body radiotherapy (SABR).

We now have the motive & the means!
BVRO-ABRO national consensus meeting.

Stereotactic radiotherapy for spinal metastases: National guidelines for Belgium

Table 3: suggested fractionation schedules and corresponding total dose:

<table>
<thead>
<tr>
<th>Suggested total dose range</th>
<th>1 fraction</th>
<th>3 fractions</th>
<th>5 fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 - 20 Gy</td>
<td>21 - 30 Gy</td>
<td>25 - 30 Gy</td>
</tr>
</tbody>
</table>
SABR for prostate cancer bone metastases.

<table>
<thead>
<tr>
<th>Study</th>
<th>Nº</th>
<th>Dose</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jereczek-Fossa et al. IJROBP 2012.</td>
<td>3</td>
<td>3x12 Gy</td>
<td>2/3 progressive within 30 months</td>
<td></td>
</tr>
<tr>
<td>Tabata K. et al. Pulm Med 2012.</td>
<td>35</td>
<td>Median 40 Gy</td>
<td>-</td>
<td>77% at 3 years</td>
</tr>
<tr>
<td>Berkovic P. et al. Clin Genitourin Cancer 2013.</td>
<td>13</td>
<td>5x10 Gy</td>
<td>Median 15 months to progression</td>
<td></td>
</tr>
<tr>
<td>Ahmed K. et al. Front Oncol 2013.</td>
<td>19</td>
<td>1 x 20 Gy</td>
<td>40% at 2 years</td>
<td>60% at 2 years</td>
</tr>
<tr>
<td>Schick U. et al. Acta Oncologica 2013.</td>
<td>25</td>
<td>Median 64 Gy</td>
<td>65% at 3 years</td>
<td>-</td>
</tr>
<tr>
<td>Muacevic A. et al. Urol Oncol 2013.</td>
<td>40</td>
<td>1 x 20 Gy</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Role of neo-adjuvant/concomitant/adjuvant ADT to eliminate microscopic disease?
SBRT can be associated with prolonged progression-free survival

Fig. 1 – Kaplan-Meier analysis depicting time to distant progression.
PSMA-PET/CT has fueled oligometastatic disease

Non-sytemic treatment for patients with low-volume metastatic prostate cancer: a randomized phase II trial.

Participating centers:
- UZ Gent
- St Lucas Gent
- Maria Middelares Gent
- UZ Leuven
- Iridium Kankernetwerk

PI: prof. dr. Gert De Meerleer (UZ Gent).
Registered on clinicaltrials.gov: NCT01558427.

www.iridiumkankernetwerk.be
Conclusions

• Modern imaging allows us to individualize salvage treatment at PSA relapse.

• To exclude local recurrence, MRI (especially with DCE sequences) is probably mandatory for PSA values > 0.5 µg/L and could be considered for lower PSA values.

• For lymph node staging, choline or PSMA PET can indicate the presence of a regional recurrence, but underestimates the extent of the disease. Salvage with surgery and/or radiotherapy should focus on whole-template, rather than focal, treatment.

• For distant staging, bone scan is only useful at high PSA levels. T2-weighted full-spine or diffusion-weighted whole-body MRI, as well as PET imaging, sometimes allow to detect so-called “oligometastases”. These could be targeted with SABR.

• Since the metastatic tumor clone arises from the primary tumor, control of the primary tumor takes on special importance in the treatment of oligometastatic, and perhaps also in polymetastatic, disease.