Definition and Management of oligometastatic hormone naive prostate cancer

Pr. JL Descotes

CHU de Grenoble
Liens d’intérêts

• Invitations à des manifestations scientifiques
  – Allergan
  – Astra Zeneca
  – Astellas
  – GSK
  – Ipsen
  – Jansen
  – Novartis
  – Pfizer
  – Pierre Fabre
  – Sanofi
  – Takeda

• Boards scientifiques
  – General electrics
  – Ipsen
  – Jansen

• Relations avec les industriels dans le cadre de la présidence de l’AFU
Localized cancer and locally advanced

70 à 80 %

Biochemical relapse after treatment

15 à 70 %

Metastatic evolution
8 + 5 years

5 % de novo metastatic disease

5 à 10 % death from disease
Clinical case n°1

- 68 years old
- First presentation
  Back pain
- PSA 1023 ng/ml
- cT3, Geason 8 (4+4)
Clinical case N° 2

• 70 years old

• Biochemical relapse 10 years after RP

• PSA = 14 ng/ml

• No symptom
Clinical case n° 3

- 85 years old
- PSA relapse after RTE
- Intermittent back pain,
  - No analgesic
  - Scintigraphy Nle
Treatment of metastatic disease (lymph nodes, visceral, skeleton) = Hormonal deprivation

However heterogeneous disease
Treatments

- Orchidectomy
- Antagonist / Agonist LHRH
- Complete androgen blockage
- Intermittent treatment
- Chemo: novantrone
- Bone targeted therapies
Metastatic disease : recent changes

• Role of Chemo (Docetaxel)
• More recently
  – Micro environnement ?
  – Immunotherapy ?
• Knowledge of Androgen Receptor biology
  – New drugs
    • Acétate d’abitarérone
    • Enzalutamide
  – New « guidelines » : EAU et AUA
• Multi disciplinary approach
Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaëlle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Priou, Benjamin Esterni, Igor Latorzef, Remy Delva, Ivan Krakowski, Brigitte Laguerre, Frédéric Rolland, Christine Théodore, Gael Deplanque, Jean Marc Ferrero, Damien Pouessel, Loic Mourey, Philippe Beuzeboc, Sylvie Zanetta, Muriel Habibian, Jean François Berdah, Jerome Dauba, Marjorie Baciuicka, Christian Platini, Claude Linassier, Jean Luc Laboure, Jean Pascal Machiels, Claude El Kouri, Alain Ravaud, Etienne Suc, Jean Christophe Eymard, Ali Hasbini, Guilhem Bousquet, Michel Soulie
Figure 2: Kaplan-Meier curves for overall survival by treatment group
Crosses indicate censoring. ADT = androgen-deprivation therapy.
• GETUG 15
  – 202 oligometastatic patients
    • 102 : ADT alone
    • 100 : Chemo + ADT

• Patients do better if low volume disease
  – 20 – 30 % die within 3-4 years

• Overall survival
  – Median 83 months in both groups
• 790 metastatic patients« chemo naive »

• Randomisation
  – 6 cycles of Docétaxel + ADT
  – ADT alone

• Global survival
  – 57,6 months Vs 44 months (HR = 0,66)

• High volume
  – 4 Osseous lésions (1 extra appendicular / or viscéral )
  – 49,2 months Vs 32,2 months (HR = 0,6)

M Hussain, Communication ASCO 2015
Global survival

M Hussain, Communication ASCO 2015
Etude Chaarted

• Oligometastatic: 277 patients
  – 3 lesions or less even if one beyond vertebrae and pelvis
    • 143: ADT alone
    • 134: chemo + ADT

• Overall survival
  – ADT alone: 4 years OS – 70%
  – Chemo + ADT: 4 years OS – 70%

Too short followup??
Pour M1 : m SG: 43 mois (S) vs 65 mois (S+D)
Bénéfice en survie globale de 22 mois
Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Claire L Vale*, Sarah Burdett*, Larysa H M Rydzewska, Laurence Albiges, Noel W Clarke, David Fisher, Karim Fizazi, Gwenaëlle Gravis, Nicholas D James, Malcolm D Mason, Mahesh K B Parmar, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Jayne F Tierney, for the STOpCaP Steering Group

2292 patients

Implications of all the available evidence
Together, these trials provide evidence that six cycles of docetaxel should be added to standard androgen deprivation therapy for men with metastatic disease commencing treatment. Men with non-metastatic disease had better prognoses, and failure-free survival was clearly improved by docetaxel; however, there were relatively few deaths in those with non-metastatic disease, so statements about overall survival in this population remain underpowered.
First line treatment of metastatic cancer

- Docetaxel + ADT
  - Offer castration combined with chemo to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy (LE: 1A; GR A)

- Castration alone
  - Offer castration alone with or without an antiandrogen to patients unfit for or unwilling to consider castration + chemo

- Castration combined with any local treatment (RT / Surgery)
  - in an investigational setting only (LE 3 GR A)
Orchiectomy
or
LHRH agonist ± antiandrogen ≥7 days to prevent testosterone flare
or
LHRH agonist + antiandrogen\(^l,u\)
or
LHRH antagonist\(^l,u\)
or
Continuous ADT\(^l,u\) and docetaxel 75 mg/m\(^2\) with or without prednisone for 6 cycles\(^v\)
No recommandation for oligometastatic patients
Necessity of revisiting our vision of metastatic disease

- Results of these recent studies
  - Sub classification

- Better survival if low metastatic volume

- Better comprehension of biology

- New tools for imaging
Biology
New concept of metastatic disease

The evolutionary history of lethal metastatic prostate cancer

Nature, 2015, 520, (7547), 353-357
Oligometastatic bone disease in prostate cancer patients treated on the TROG 03.04 RADAR trial

Swetha Sridharan\textsuperscript{a}, Allison Steigler\textsuperscript{b}, Nigel A. Spry\textsuperscript{c}, David Joseph\textsuperscript{c}, David S. Lamb\textsuperscript{d}, John H. Matthews\textsuperscript{e}, Chris Atkinson\textsuperscript{f}, Keen-Hun Tai\textsuperscript{g}, Gillian Duchesne\textsuperscript{g}, David Christie\textsuperscript{h}, John Attia\textsuperscript{b,i}, Elizabeth G. Holliday\textsuperscript{b,i}, James W. Denham\textsuperscript{b,*}

\textsuperscript{a}Calvary Mater Newcastle, Waratah; \textsuperscript{b}School of Medicine and Public Health, University of Newcastle; \textsuperscript{c}Sir Charles Gairdner Hospital, Perth, Australia; \textsuperscript{d}Wellington Cancer Centre; \textsuperscript{e}Auckland Hospital; \textsuperscript{f}St. George's Cancer Care Centre, Christchurch, New Zealand; \textsuperscript{g}Peter MacCallum Cancer Centre, Melbourne; \textsuperscript{h}GenesisCare, Tugun; and \textsuperscript{i}Hunter Medical Research Institute, Newcastle, Australia

\textbf{Fig. 1.} Evidence of a prostate cancer-specific mortality gradient in men with solitary, two or three, and more than three bony metastatic presentations ($n = 1071$). Abbreviations: BM, bony metastasis.
Fig. 2. Evidence that non-bony sites of progression at or prior to diagnosis of bony metastasis also contribute to the prostate cancer-specific mortality gradient ($n = 1071$). Abbreviations: BM, bony metastasis.
These data lead to identifying the concept of Oligometastatic disease
Oligometastatic disease
2 main questions

1. Definition

2. Management
Definition

• Based on the number of metastatic lesion?

• Based on the sites of metastatic lesions?

• Or is it a question of:
  – natural history
    • survival differences
  – ability to treat all visible lesions?
Definition of oligometastatic disease

• Not a unique entity
  – Prostate gland treated
  – Prostate gland intact

• No clear definition
  – Tumor burden: huge variability

• No clear treatment
  – Is it really a systemic disease?
An heterogeneous disease

• Define clearly the burden of the extension of the disease
  – Lymph nodes
  – Bones
  – Visceral

• Biology:
  – PSA; Phosphatases alcalines..
  – Waiting for other markers

• Histologic evaluation
  – Gleason, Neuroendocrine differenciation
    – For the primitive lesion and / or metastatic lesions

Variations are function of imaging modalities
An heterogeneous disease

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  – Bones
  – Visceral

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  – PSA; Phosphatases alcalines..
  – Waiting for other markers

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An heterogeneous disease

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• Histologic evaluation
  – Gleason, Neuroendocrine differenciatiation
    – For the primitive lesion and / or metastatic lesions
Oligometastatic disease: which imaging tool?

- Based on clinical trials?
  - SWOG; Chaarted; GETUG 15

- Based on conventional imaging?
  - CT / IRM
  - Tc Scintigraphy

- Based of new modalities of imaging
  - PET CT
  - Whole MRI
Consensus for definition

St Gallens (Gillessen Ann Oncol 2015)

- No visceral disease (lung or liver)
- No disease beyond the appendicular skeletal (SWOG definition)
- Lymph node disease is frequent
- 2 or 3 axial osseous lesions
  - Vertebreae
  - Pelvis
Definition of tumor burden will probably move quickly

- Tc Bone Scintigraphy + CT scan
- Novel imaging
  - Whole body MRI
  - Choline PET
  - PET / MRI
  - PSMA
  - NaF PET
- More lesions: micrometastatic lesions
  - New entity? Stage migration?
## Imaging: a lot of work

<table>
<thead>
<tr>
<th></th>
<th>Strengths</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT Scan</strong></td>
<td>Widely available</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td>Easily standardised</td>
<td>Limited local disease evaluations</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>Subcentimetre nodal characterisation</td>
</tr>
<tr>
<td></td>
<td>Trial guidelines</td>
<td>CT flare</td>
</tr>
<tr>
<td><strong>Bone scan</strong></td>
<td>Widely available</td>
<td>No ability to assess soft tissue disease</td>
</tr>
<tr>
<td></td>
<td>Easily standardised</td>
<td>Lower sensibility / specificity than CT/MRI</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>Does not directly evaluate malignat bone disease : osteoblastic uptake</td>
</tr>
<tr>
<td><strong>Pet CT Choline</strong></td>
<td>High sensitivity relatively good specificity</td>
<td>Limited tracer availability</td>
</tr>
<tr>
<td></td>
<td>Objective response parameters (SUV)</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non accurate for liver and urinary lesions</td>
</tr>
<tr>
<td><strong>Whole body MRI</strong></td>
<td>Flexible; adaptable imaging</td>
<td>longer acquisition time</td>
</tr>
<tr>
<td></td>
<td>Objective response parameters</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expertise and competing demands</td>
</tr>
</tbody>
</table>
Other tracers

- 18 F – FACBC PET/CT
- 68Ga-PSMA PET/CT  
  - Salvage treatments
- 18F DCFPylis PET / CT  
  - Salvage treatments
- 18 F Bombesin PET / CT  
  - Active surveillance

- Lack of studies
Rationale for Modernising Imaging in Advanced Prostate Cancer

Anwar R. Padhani\textsuperscript{a,*}, Frederic E. Lecouvet\textsuperscript{b}, Nina Tunariu\textsuperscript{c}, Dow-Mu Koh\textsuperscript{c}, Frederik De Keyzer\textsuperscript{d}, David J. Collins\textsuperscript{c}, Evis Sala\textsuperscript{e}, Stefano Fantil\textsuperscript{f}, H. Alberto Vargas\textsuperscript{e}, Giuseppe Petralia\textsuperscript{g}, Heinz Peter Schlemmer\textsuperscript{h}, Bertrand Tombal\textsuperscript{i}, Johann de Bono\textsuperscript{j}

\textbf{Evidence synthesis:} Meta-analyses showed that positron emission tomography (PET)/CT with different radiotracers and whole-body magnetic resonance imaging (WB-MRI) are more accurate for bone lesion detection than CT and bone scans (BSs). At a patient level, the pooled sensitivities for bone disease by using choline (CH)–PET/CT, WB-MRI, and BS were 91\% (95\% confidence interval [CI], 83–96\%), 97\% (95\% CI, 91–99\%), and 79\% (95\% CI, 73–83\%), respectively. The pooled specificities for bone metastases detection using CH–PET/CT, WB-MRI, and BS were 99\% (95\% CI, 93–100\%), 95\% (95\% CI, 90–97\%), and 82\% (95\% CI, 78–85\%), respectively. The ability of PET/CT and WB-MRI to assess therapeutic benefits is promising but has not been comprehensively evaluated. There is variability in the cost, availability, and quality of PET/CT and WB-MRI.
Imaging and evaluation of therapeutic response (HT)

![Diagram showing the process of prostate cancer diagnosis, staging, treatment options, and evaluation of therapeutic response.]

Fig. 2 - Flow-chart of the diagnostic management of prostate cancer patients. ADT = androgen therapy; BRT = brachytherapy; CT = chemotherapy; EBRT = external beam radiotherapy; PSA = prostate specific antigen; PSMA = prostate specific membrane antigen; RP = radical prostatectomy; sLND = salvage lymphadenectomy.
3. Do we need to manage differently

- Local treatment?
  - With or without ADT

- Treatment of all metastatic lesions?
  - Surgery / RT

- ADT alone
  - + HT 2eme

- Chemo + ADT
Treatment choice

- Age, global status, voiding and sexual function
- Symptômes induced by metastatic diffusion
- Cardiovascular evaluation
  - « Règle ABCDE »
- Metabolic syndrom
- Skeleton related events
  - Ostéoporosis ?
Management of oligométastatic disease

1. Is there a role for:
   1. Lymph node surgery
   2. Prostatectomy surgery

2. Is there a place for RT
Clinical implications of cancer self-seeding

Elizabeth Comen, Larry Norton and Joan Massagué

Kadmon et al J Urol 1982;127
- 369 pts T1-T3aN0M0, RTE 65 Gy suivis 10 ans dont 74 (20 %) devenus M+ en cours de suivi

- Survie selon nb méta os:
  - ≤ 5 : 73% et 36% à 5 et 10 ans
  - > 5 : 45% et 18 %

- Délai de 4,9 ans vs 3,3 ans au diagnostic de M+ osseuse si +/- 5M+

Singh et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases?. IJROBP (2004) vol. 58 (1) pp. 3-10
## Local treatment in pN+

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Castration</th>
<th>10 yr OS ADT Alone</th>
<th>10 yr OS w/ADT + RP or EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghavamian</td>
<td>1998</td>
<td>Yes</td>
<td>28%</td>
<td>66%</td>
</tr>
<tr>
<td>Engel</td>
<td>2010</td>
<td>Yes</td>
<td>28.2%</td>
<td>63.8%</td>
</tr>
<tr>
<td>Zagars</td>
<td>2001</td>
<td>Yes</td>
<td>46%</td>
<td>67%</td>
</tr>
<tr>
<td>Steuber</td>
<td>2010</td>
<td>Yes (90%)</td>
<td>42%</td>
<td>69%</td>
</tr>
<tr>
<td>ECOG 3886</td>
<td>2006</td>
<td>Yes</td>
<td>NA</td>
<td>64%</td>
</tr>
<tr>
<td>EORTC 30846</td>
<td>2009</td>
<td>Yes</td>
<td>25%</td>
<td>NA</td>
</tr>
<tr>
<td>Touijer</td>
<td>2013</td>
<td>No</td>
<td>NA</td>
<td>60%</td>
</tr>
</tbody>
</table>

Ghavamian et al J Urol 98 161:1223-1228  
Engel et al Eur Urol 57 (2010) 754-761  
Zagars et al Urology 258 (2001) 233-239  
Steuber et al BJUI 2010 107, 1755-1761  
Touijer, Eur Urol 2013
RP in pN+ disease

• 30 – 45 % improved overall survival in patients treated with RP (Verhagen et al, Eur Urol, 2010)
  • Cadeddu et al, 1997
  • Ghavamian et al, J Urol, 1999
    – CSS 40 vs 80 %; OS : 30 vs 65 % at 10 years
  • Engel et al, Eur Urol, 2010, ……

• Improves risk stratification
  • Moschini, J Urol, 2016

• Differ hormonal therapy (pN+ <=2)
  • Toujier, Eur Urol 2014
Lymph node micro invasion: Réduction du risque local

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Local Symptomatic Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frazier (N+)</td>
<td>1994</td>
<td>156</td>
<td>24.6%</td>
</tr>
<tr>
<td>Wiegand (N+)</td>
<td>2010</td>
<td>192</td>
<td>44.6%</td>
</tr>
</tbody>
</table>

Improvement in symptomatic progression may be reason alone for providing local treatment

A real benefice

Wiegand. BJUI 107 (2010) 1238-1242
Salvage lymphadenectomy

• A third of radical prostatectomy experience biochemical recurrence

• 11 C – Choline
  – More favorable pronostic after exereze
    • 50 % DFP at 5 years
  – Acceptable morbidity
    • Abdollah, Eur Urol 2014
Oligometastatic patients
Is there a role of prostate surgery

• All series: Selected patients
  – Number of biases

• However surgery may improve
  – Local control
  – Survival (kidney, colon)
  – Response to ADT (N+)

  • Messing...
Radical prostatectomy in metastatic patients: survival

Control of the primary tumor is linked to longer survival in men with metastatic prostate cancer.


Fig. 1 – Survival of patients in the Munich Cancer Registry who did and did not undergo radical prostatectomy: (a) patient cohort, 1998–2010; (b) overall survival in M1 prostate cancer patients.
ADT = androgen deprivation therapy; RP = radical prostatectomy; RPE = extraperitoneal radical prostatectomy; XRT = external-beam radiation therapy.
Prostate Cancer

Radical Prostatectomy in Men with Oligometastatic Prostate Cancer: Results of a Single-institution Series with Long-term Follow-up

- 11 Patients
- Followup 7 years
  - N+ 10 patients; Positive margins 8 patients
  - Multi modal approach (RT + HT)
- 2 died at 7 years (20 % cancer specific mortality)
Radiotherapy for oligometastatic patients

Concept:
• Curative intent of all metastases
• Local control
• Immunological effect (effet abscopal)

N = 25 patients
• Contrôle local à 3 ans: 90%
• Toxicité G2+ = 0
• Pelvic, paraaortic Mediastinal LN

Casamassima et al. Tumori 2011
Condition for local radiation therapy

- Traitement of all metastatic lesions
- Stereotactic radiotherapy is mandatory
  - High dose per fraction
  - Better targeting
  - Safer (prevent lesion adjacent organ at risk)
  - Feasible
- Multileaf collimator
- Cyberknife
- Image fusion; immobilisation of patients
Stereotaxy

- To limit morbidity
- Tracking
- High dose
- Focused treatment
Platinum Priority – Brief Correspondence

Editorial by Vincent Khoo on pp. 13–14 of this issue

Progression-free Survival Following Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Treatment-naive Recurrence: A Multi-institutional Analysis

Piet Ost\textsuperscript{a,}, Barbara Alicja Jereczek-Fossa\textsuperscript{b}, Nicholas Van As\textsuperscript{c}, Thomas Zilli\textsuperscript{d},
• 119 patients with 163 metastases
  – One : 72,3%; Two 18,5 %; Three : 9,2 %
  – Lymph node : 60%; Bone 36%
• Irradiation of metastatic sites
  – 80 gy to 140 gy
• Distant progression free survival
  – 30 % at 3 years
  – 15 % at 5 years
• Overall survival : 88 % at 5 years
Potential Indications

• Oligometastatic disease
  – Small lesions

• Whom ?
  – Oligometastatic ≠ oligorecurrence ≠ oligoprogressive
  – Good performance status
  – Symptomatic lesions with no response to ADT ?
    • ≠ Palliative role

• Why :
  – Delay disease progression and time to palliative ttt: no answer
  – Limit hormon deprivation (side effects)

Ost 2016
Berkovic 2012
Few results in the literature

- Muracevic, 2013
  - 40 patients
    - 75 : single location
    - Mean follow-up short : 14 months

- Brignanti : 2011
  - Solitary met : better progression free survival

- Prospective Trials++
Salvage Treatment or Active Clinical Surveillance for Oligometastatic Prostate Cancer: a Randomized Phase II Trial (NCT01558427)

Active clinical surveillance
- Active monitoring of patients with low volume metastases with PSA and sequential imaging.
- Procedure: Surveillance
- Active clinical surveillance

Salvage treatment of metastases
- Surgical or radiotherapy treatment of metastases.
- Procedure: Surgical removal of metastases, or stereotactic body radiotherapy of metastases.

**Primary Endpoint:** ADT free-survival

**Secondary Endpoint:** QOL

Piet Ost – Ghent University hospital
Summary

- Dogma has changed
- Multidisciplinary approach
- Better identify candidates: Trials +++
- Genenics and molecular imaging
Summary

• Some patients with « conventional high risk disease » were probably oligometastatic
  – (if we consider new imaging ) and cured

• If micro met are very ADT dependant, local therapy + ADT +/- non AR therapy could improve survival

• Understand biology is waranted

• Role of docetaxel for these patients : unknown
  – Think quality of life