

**Prostate brachytherapy,  
UK and Ireland Conference 2015**

**New and future techniques :  
the French experience of focal  
Brachytherapy**

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## « Focal therapy » for prostate cancer

- Just a new « fashionable » technique ?
- Or a reasonable compromise, for selected patients, between :
- « Not enough » ( Active Surveillance) ?
- « Too much » ( Treatment, whatever it is, of the WHOLE prostate ...) ?
- See : Uri Lindner, CUAJ, 2009, Vol.3, 4, 333-335 ;  
*« Focal therapy for localized prostate cancer ,  
choosing the middle ground »*

In 2015, it may be time to «revisit»  
the dogma of the treatment of **the**  
**whole** prostate ??

- Percentage of « unifocal » tumour after prostatectomy ;
- Eggener, J.Urol, 2007 ; **13 - 38 %**
- Weissman, PCRI insights, 2008; **15 - 40 %**
- Moreover:
- The Concept of « Index or largest tumor »  
( Scardino, Nature Reviews Urology, 2009)

# The Concept of « Index » or largest tumor :

- In most cases: this « index » ( or largest ) tumor represents more than 90 % of the total tumor volume ( Ohori 2006; AUA , N° 1574)
- Other lesions ; microfoci !
- With 80 % of those microfoci < 0.5 ml !...
- A ( provocative ?) hypothesis :
- *treating or not those microfoci will not change survival ...*

## Considering those data, and:

- **The poor acceptance of active surveillance by some patients ( and some countries ...)**
- **The need to bring an answer to the accusations of « overtreatment(s) » ...**
- **The low expected toxicity of the « focal » therapies (?)**
- **The increased possibilities of a « salvage treatment » after a focal therapy (?)**

**« Focal therapy » of prostate  
cancer is more and more  
often discussed in 2015**

- An impressive number of papers in 2014 !!

- Curr Opin Urol. 2014 May;24(3):270-9.
- **Management of low risk prostate cancer: active surveillance and focal therapy.**
- Klotz L<sup>1</sup>, Emberton M.
- Curr Opin Urol. 2014 May;24(3):231-5.
- **Focal radiotherapy as focal therapy of prostate cancer.**
- Kovács G<sup>1</sup>, Cosset JM, Carey B.
- Nat Rev Clin Oncol. 2014 Apr 22.
- **Can we deliver randomized trials of focal therapy in prostate cancer?**
- Ahmed HU<sup>1</sup>, Berge V<sup>2</sup>, Bottomley D<sup>3</sup>, Cross W<sup>3</sup>, Heer R<sup>4</sup>, Kaplan R<sup>5</sup>, Leslie T<sup>6</sup>, Parker C<sup>7</sup>, Relton C<sup>8</sup>, Stephens R<sup>9</sup>, Sydes MR<sup>5</sup>, Turnbull L<sup>10</sup>, van der Meulen J<sup>11</sup>, Vickers A<sup>12</sup>, Wilt T<sup>13</sup>, Emberton M<sup>1</sup>; the Prostate Cancer RCT Consensus Group.
- Eur Urol. 2014 Jun;65(6):1078-83.
- **Focal therapy in prostate cancer: international multidisciplinary consensus on trial design.**
- van den Bos W<sup>1</sup>, Muller BG<sup>2</sup>, Ahmed H<sup>3</sup>, Bangma CH<sup>4</sup>, Barret E<sup>5</sup>, Crouzet S<sup>6</sup>, Eggener SE<sup>7</sup>, Gill IS<sup>8</sup>, Joniau S<sup>9</sup>, Kovacs G<sup>10</sup>, Pahernik S<sup>11</sup>, de la Rosette JJ<sup>2</sup>, Rouvière O<sup>12</sup>, Salomon G<sup>13</sup>, Ward JF<sup>14</sup>, Scardino PT<sup>15</sup>.
- Aging Male. 2014 Mar 6
- **Supporting prostate cancer focal therapy: a multidisciplinary International Consensus of Experts ("ICE").**
- Reis LO<sup>1</sup>, Billis A, Zequi SC, Tobias-Machado M, Viana P, Cerqueira M, Ward JF. **Etc ...**

Just released:

**« Technical aspects of focal therapy in localized prostate cancer »**

- Eric Barret, Matthieu Durand, *editors*
- ***Springer***



# With discussions !...

- Curr Opin Urol. 2014 May;24(3):247-55.
- **What is still needed to make focal therapy an accepted segment of standard therapy?**
- van den Bos W<sup>1</sup>, Muller BG, Ehdaie B, Scardino P, de la Rosette JJ.
- J Clin Oncol. 2014 May 1;32(13):1299-301. **Will focal therapy remain only an attractive illusion for the primary treatment of prostate cancer?**
- Giannarini G<sup>1</sup>, Gandaglia G, Montorsi F, Briganti A.

# A landmark :

- *BJU INTERNATIONAL 2012,109,SUPPLEMENT 1,7–16*

- **Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer**

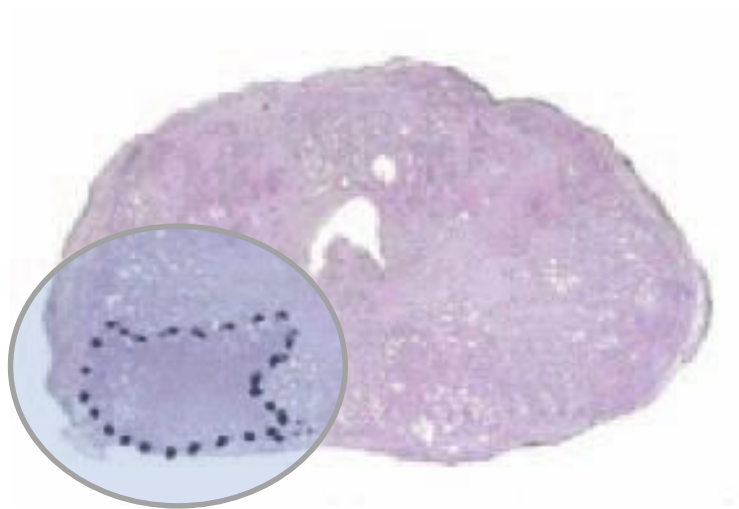
**Stephen Langley<sup>1</sup>, Hashim U. Ahmed<sup>2</sup>, Bashar Al-Qaisieh<sup>3</sup>,  
David Bostwick<sup>4</sup>, Louise Dickinson<sup>2</sup>, Francisco Gomez Veiga<sup>5</sup>,  
Peter Grimm<sup>6</sup>, Stefan Machtens<sup>7</sup>, Ferran Guedea<sup>8</sup> and Mark Emberton<sup>2</sup>**

- *1Department of Urology, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK, 2Division of Surgery and Interventional Science, University College London, UK, 3Medical Physics Department, StJames's Institute of Oncology, Leeds, UK, 4Bostwick Laboratories, Virginia, USA, 5Department of Urology, Complejo Hospitalario Universitario, La Coruña, Spain, 6Prostate Cancer Treatment Center of Seattle, USA , 7Department of Urology, Marien-Krankenhaus, Bergisch Gladbach, Germany, and 8Department of Radiation Oncology, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain*

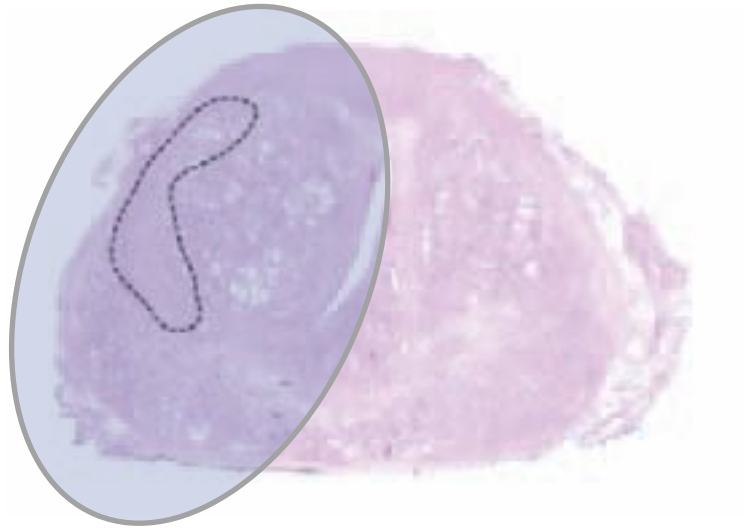
- *“It is anticipated that these consensus findings will provide teams currently conducting prostate brachytherapy with **guidance on patient selection for focal brachytherapy and recommendations** for how the technique should be conducted...”*
- *“Future papers from this international committee will provide more specific recommendations on dosimetry and plan a roadmap forward to conduct the **phase II randomized comparative study** in a timely manner that would derive early results in order to benefit men with prostate cancer...”*

# Definitions

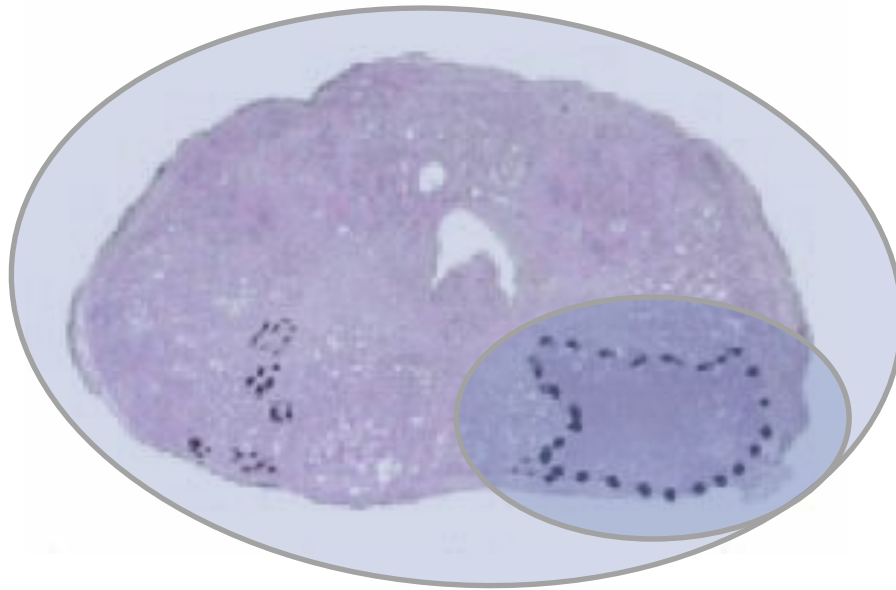
- **Ultra-focal therapy :**



- **Focal therapy ; hemi-gland**



- **Focused therapy ( Differential)**



- ***TABLE 3 Consensus findings on patient selection for focal therapy***

- **1. Life expectancy >10 years**
- **2. PSA  $\leq 15$  ng/mL**
- **3. Multi-parametric (T1W/T2W, diffusion-weighting, dynamic contrast enhancement  $\pm$  spectroscopy) magnetic resonance imaging prior to biopsy**
- **4. Bilateral template-guided prostate mapping biopsy with 5 mm sampling frame**
- **5. Unilateral disease; lesion size  $\leq 0.5$  mL (approximately equates to maximum cancer length of 10 mm) with or without clinically insignificant disease on the contralateral side (cancer core length  $\leq 3$  mm)**
- **6. Gleason score of index lesion 6–7 (3 + 4)**
- **7. Tumour stage  $\leq$  T2b**
- **8. Prostate size  $\leq 60$  mL**

- ***TABLE 6 Consensus findings on a focal brachytherapy clinical trial protocol: follow-up***

- 1. Template prostate mapping biopsy (5 mm sampling frame) of treated and untreated tissue
- 2. PSA monitoring at 3-month intervals in year 1 and then 6 monthly
- 3. Biochemical progression free survival: options include Phoenix definition (nadir + 2), PSA doubling time, percentage free/total PSA
- 4. mpMRI prior to biopsy
- 5. Functional outcomes to be assessed using patient urinary diaries and patient questionnaires: IPSS, EPIC, SF-36, IIEF-15, EORTC QLQ C30, EORTC QLQ Pr25, Euro QOL, pain score
- 6. Health economics



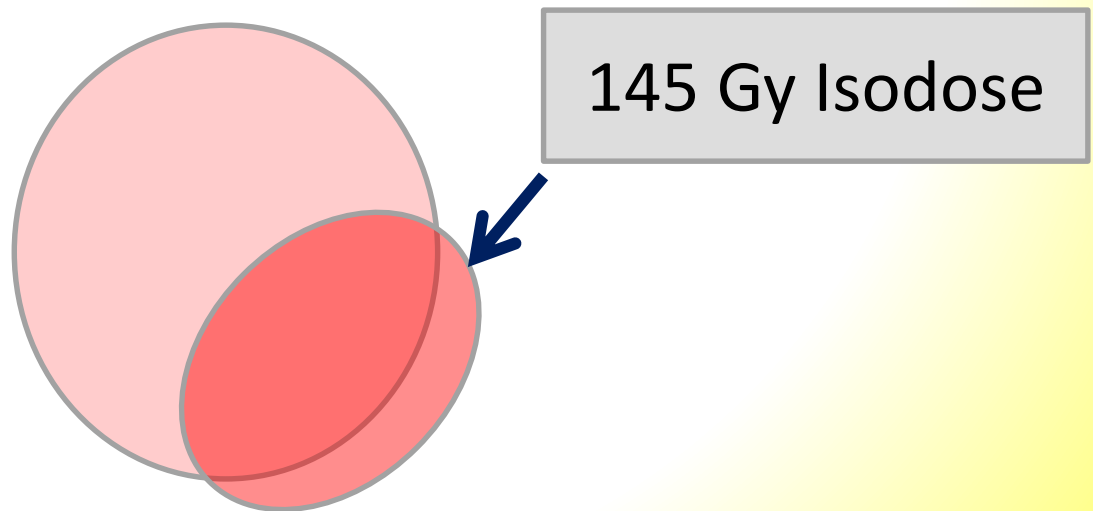
# **A main point ; The patient selection**

- For most involved centers ;
- Selection mainly based on :
- Transperineal biopsies ( cartography ): more than 20 ...
- Endorectal MRI + spectroscopy when possible ( multiparametric MRI)

# Which technique ?

- See for example : Weissman 2008 and the Barret and Durand book 2015 ;
- Cryotherapy
- HIFU
- Photodynamic therapy
- Laser activated nanoparticles
- **Focal brachytherapy**
- *And a few others ...*

- Potential advantages for brachytherapy when compared with the other « focal » techniques :
- Brachytherapy is able to « cover » **3 to 4 mm** **outside the capsule** :



## Moreover ...

- Brachytherapy offers **a precise distribution of a precise dose ;**
- While most other techniques are lacking such a precise dosimetry ...

# Consequently,

- Brachytherapy, which is able to treat a well-defined partial prostate volume at a well-defined dose level,
- therefore appears to be particularly well adapted to focal prostate therapy !

# The French experience

- In Paris, since 2006 : close collaboration between the radiotherapy department of the Institut Curie and the Urology department of the Institut Mutualiste Montsouris ( IMM );
- To date :
- Overall : more than **400 focal treatments** performed at the IMM, essentially using:
- Photodynamic therapy
- HIFU ( ultrasounds)
- Cryotherapy
- **Brachytherapy**

- **Morbidity of focal therapy in the treatment of localized prostate cancer.**
- *Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, Macek P, Durand M, Prapotnich D, Rozet F, Cathelineau X.*
- *Eur Urol. 2013 Apr;63(4):618-22.*
- **TOOKAD(®) Soluble vascular-targeted photodynamic (VTP) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer.**
- *Azzouzi AR, Barret E, Moore CM, Villers A, Allen C, Scherz A, Muir G, de Wildt M, Barber NJ, Lebdaï S, Emberton M.*
- *BJU Int. 2013 Oct;112(6):766-74*
- **Focal cryoablation: a treatment option for unilateral low-risk prostate cancer.**
- *Durand M, Barret E, Galiano M, Rozet F, Sanchez-Salas R, Ahallal Y, Macek P, Gaya JM, Cerruti J, Devilliers H, Loeffler J, Amiel J, Vallancien G, Cathelineau X*
- *BJU Int. 2014 Jan;113(1):56-64.*

- In Paris, **focal brachytherapy was initiated in February 2010,**
- According to a protocol approved by the IMM ethics committee, with all patients receiving detailed information and signing an informed consent.



- In this Phase II non-randomized study,
- Patient selection is based on (at least) **two series of prostate biopsies ( with a minimum of 20 biopsies overall)**
- **and on a high-resolution endorectal MRI.**
- Only patients with very limited and localized tumors, according to strict criteria, ( *actually almost the same as in the “consensus” paper* ), were selected for the procedure.

- The entry criteria being almost identical to the French active surveillance's ones,
- **All patients were proposed active surveillance**, but they expressed their ( written ) will to choose focal treatment.
- Among those patients referred to our group for discussion of a focal brachytherapy, only 2 chose the surveillance strategy ( *but clear selection of patients*)...

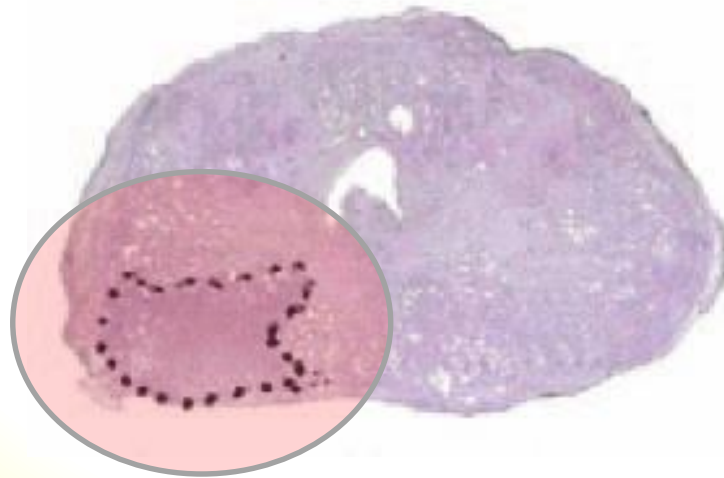
- The technique is directly derived from the “real-time” procedure (already published by our team) with the permanent implantation of “free” LDR 125 Iodine seeds,
- The reason for the choice of the I 125 seeds:
- An experience of more than 3300 patients implanted with 125 I seeds since 1998 by our group,
- **And** the recommendations of the 2012 BJU Consensus paper :
- *“When reviewing the characteristics of the different permanent seed isotopes available (125I, 103Pd and 131Cs) it was noted that 125I had the most favourable characteristics”*

- The reasons for the choice of a permanent-implant free-seed technique :
- Again, our experience of more than 3300 treated patients,
- And again, the recommendations of the 2012 consensus paper:
- *“The greater flexibility afforded by loose seeds may be important for implanting the central portion of the prostate as in a hemi-gland implant.”*
- *“For the ultra-focal protocol, loose seeds might be preferable.”*

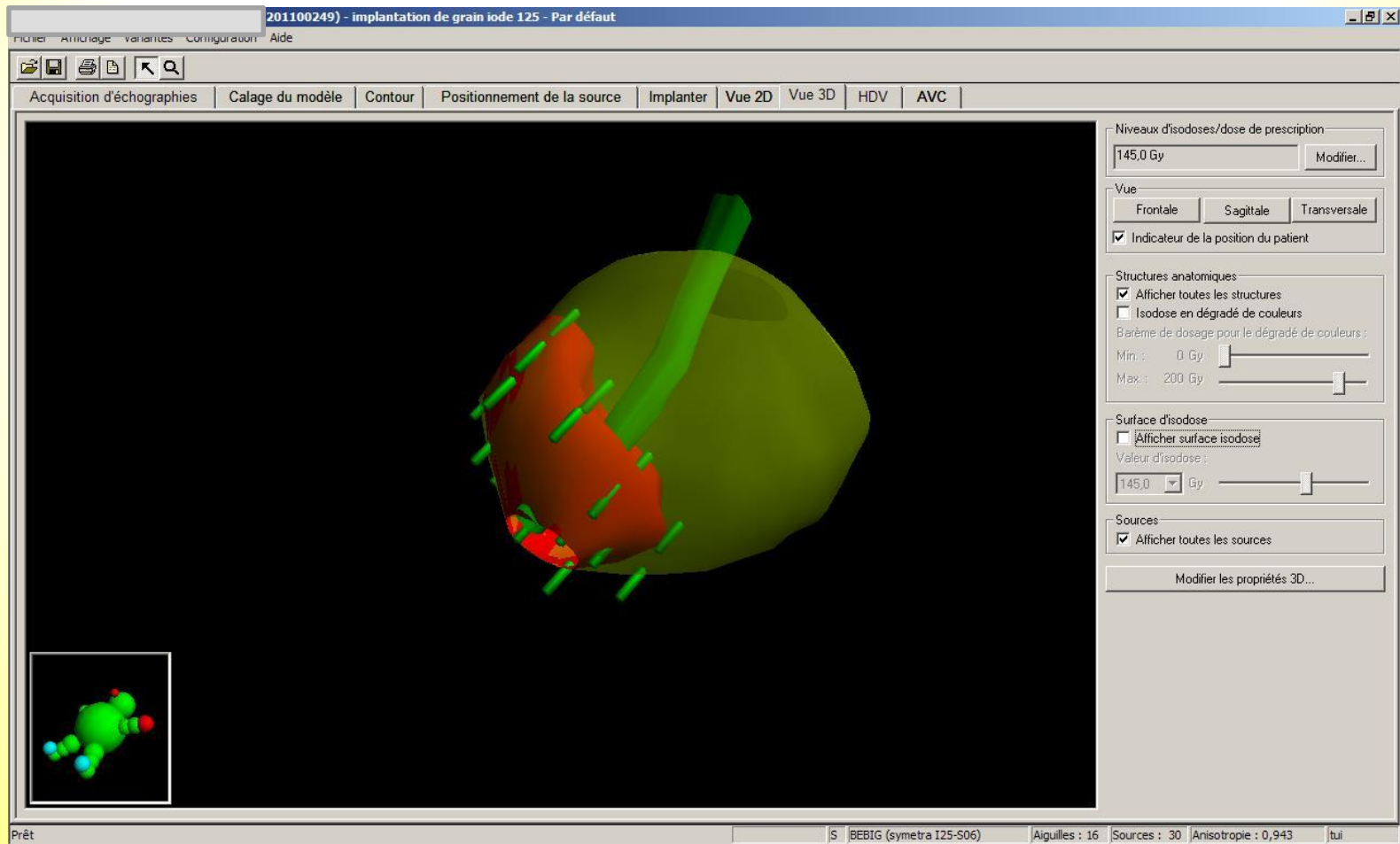
- We chose to deliver to the focal volume the dose usually recommended by the GEC-ESTRO for the whole prostate (145 Gy).
- Sticking to the same dose constraints to the surrounding structures : see :
- *Tumour and target volumes in permanent prostate brachytherapy: the ESTRO/EAU/EORTC recommendations on prostate brachytherapy.*
- *Salembier C, Lavagnini P, Nickers P, Mangili P, Rijnders A, Polo A, Venselaar J, Hoskin P; GEC ESTRO PROBATE Group.*
- *Radiother Oncol. 2007 Apr;83(1):3-10*

# Finally,

- **Considering our ( severe ) selection of patients,**
- **We chose to propose, in most cases, the « ultra-focal » technique, with a margin of about 10 mm around the MRI target.**



**First step ; Choice of the « focal » Volume,  
based whenever possible on a MRI-echography fusion**





- **Second step** ; Complete real-time preplanning
- **Third step** : Implantation of needles
- **Fourth step**: Implantation of seeds, according to the preplanning, with continuous feed-back taking into account the real position of each seed ( « dynamic dosimetry »).

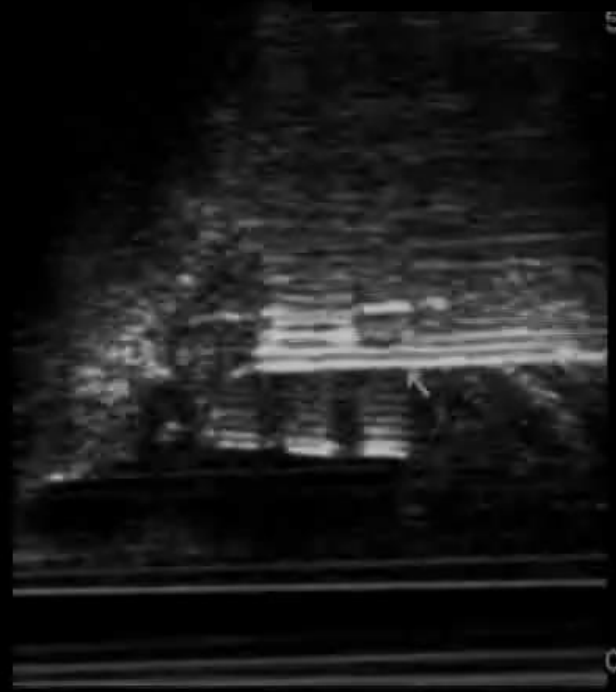


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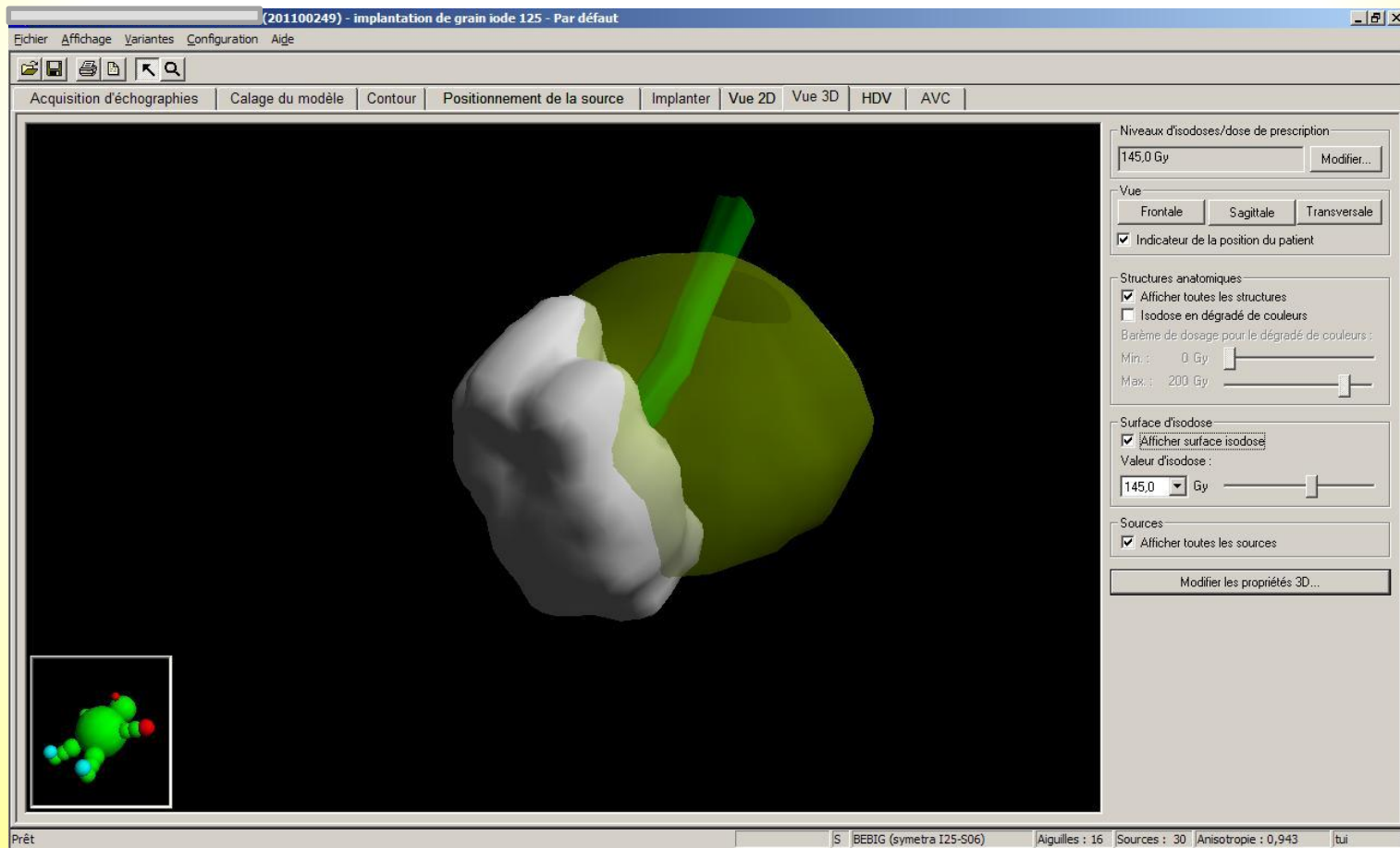
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# **Fifth step : Dosimetric results ;**

## **In white: the 145 Gy isodose**



# Preliminary results

## • **Focal brachytherapy for selected low-risk prostate cancers: a pilot study.**

- **Jean-Marc Cosset<sup>1,2</sup>, Xavier Cathelineau<sup>2</sup>, Georges Wakil<sup>1,3</sup>, Noelle Pierrat<sup>1</sup>, Olivier Quenzer<sup>4</sup>, Dominique Prapotnich<sup>2</sup>, Eric Barret<sup>2</sup>, François Rozet<sup>2</sup>, Marc Galiano<sup>2</sup>, Guy Vallancien<sup>2</sup>**

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- <sup>2</sup> Department of Urology, Institut Mutualiste Montsouris, 75013 Paris, France
- <sup>3</sup> Department of Radio-Oncology, Hospital Charles LeMoyne, Montréal, Canada
- <sup>4</sup> Department of Statistics, Institut Curie, 75005 Paris, France
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- **Brachytherapy, 2013, 12, 331-337**

# In this first series :

- **21 focal implantations** were performed and analyzed,
- *(To date -March 2015- : 48)*
- The treated volume corresponded to a **mean value of 35% of the total prostatic volume (range 20-48 %).**
- For the focal volume, **mean D90 was 182 Gy, and the mean V100 was 99.6 %.**

- In our experience, the technique could be entirely performed in approximately **an hour and a half**, that is to say not significantly different from a usual “whole prostate” brachytherapy.
- Early urinary toxicity ( still being evaluated) seems to be somewhat ***inferior*** to what is usually observed after brachytherapy of the whole prostate.

- **Table 1 : Urinary toxicity ( scored by IPSS) and sexual toxicity (scored by IIEF5) for focal prostate brachytherapy. *Incontinence score ( ICS) and rectal toxicity ( almost constantly nil in this series ) not shown.***
- Mean ( range)
- **Initial IPSS** **5.3** (0-15)
- IPSS at 2 months 11.8 (1-28)
- IPSS at 6 months 6.6 (2-17)
- IPSS at 12 months **5.4** (2-9)
- **Initial IIEF5** **18.2** (1-25)
- IIEF5 at 2 months 16.6 (1-25)
- IIEF5 at 6 months 17.7 (1-25)
- IIEF5 at 12 months **18.3** (1-25)

- we did compare the toxicities observed in this first series of focal brachytherapy with the ones that were registered in a series of 100 patients treated by a “whole prostate” brachytherapy by our group in the same institution ( Institut Mutualiste Montsouris) , and analyzed with the same questionnaires
- ( **Questionnaires filled in by the patient himself and NOT by the physician ).**

- **Since almost no change in the ICS score nor in the rectal toxicity score was noted in both series, we concentrated on the evolution of IPSS and IIEF.**



- We first checked that the two groups ( “Focal” and “total”) were **comparable** in terms of initial IPSS (  $p=0.95$ ) and initial IIEF ( $p=0.51$ ).
- In both groups, we analyzed the **mean scores** at 2, 6 and 12 months, and also the **variations** of these scores ( comparing the scores at distance with the initial values).

- **For IPSS**, the mean scores and variations were comparable at 2 and 12 months in both groups, focal and total, *but there was a borderline difference favoring the “focal” group at 6 months*,
- *both in terms of direct comparison of the mean scores (  $p=0.04$ ) and in terms of variation compared with the initial values ( $p=0.05$ ).*

- **For erectile toxicity (IIEF)**, we did not observe any significant difference between the mean scores in the “focal” and “total” groups at 2, 6 and 12 months (  $p=0.43$  ;  $p=0.46$  ;  $p=0.17$  respectively),
- ***but the re-increase of the score was significantly better in the focal group at 6 and 12 months ( $p=0.014$  et  $p=0.012$ , respectively).***

## Update 2015 : A trend ?

- With now 48 patients implanted ( focal ):
- Possible trend for **less early urinary toxicity after focal implantation of the apex**
- Compared with an implantation of the prostate base (?)

## Update 2015

	Mean IPSS 2 months	Mean IPSS 6 months
<b>All cases</b>	<b>11.4</b>	<b>8</b>
<b>Focal base</b>	<b>13.4</b>	<b>10.1</b>
<b>Focal apex</b>	<b>9.9</b>	<b>6.7</b>

**To be confirmed ...**

# Update 2015

- **Control biopsies** ; planned between 18 and 24 months post-implantation,
- 24 Patients accepted the control biopsies ( 10 to 28 cores) : 6 patients refused ...
- **In 21/24 cases ; control biopsies were negative,**
- **In 3 cases ; Controlateral positive biopsies**

## 3 positive control biopsies at 2 years

- - **1 case** ; 1 contralateral microfocus ; active surveillance, but MRI relapse at 4 years ; biopsies planned
- - **1 case** ; 2 contralateral positive biopsies ; *contralateral complementary focal brachytherapy*. Alive and well.
- - **1 case** ; 1 contralateral positive biopsy; being explored.

## Moreover :

- - 1 nodal ( iliac) relapse at 1 year ½ ; hormone therapy.
- - 1 relapse at ( controlateral) biopsies performed at 3 years ½ ( *while the 2 years control biopsies were negative*); T3 MRI ; **radio-hormonotherapy**.
- 1 case suspect ++ of homolateral relapse on MRI at 3 years ( just above the treated focal volume) with a rising PSA ; targeted biopsies planned.



# Overall : update 2015

- Among 48 patients , 30 with a follow-up > 2 years.
- No relapse in the treated focal volume
- 6 relapses have been registered:
- 1 nodal
- 4 contralateral
- 1 homolateral above the previously treated volume

# Conclusion:

- **The French experience on 48 patients :**
- **Focal prostate treatment by brachytherapy is easily feasible,**
- **With apparently little acute urinary toxicity ( essentially when treating the apex ?)**
- **No relapse in the treated area ( among 48 patients), BUT 6 relapses / 48, with a relatively short follow-up : too much ?**

- Therefore : non-negligible relapse rate outside the treated volume ,
- In spite of the relatively short follow-up
- and of the severe selection of patients in this series ...
- Tentative conclusion : **PRUDENCE ...**

- Further investigation is needed to more precisely assess the long-term tumor control rate,
- Taking into account the possibility and efficacy of salvage therapies ...