Radiothérapie en conditions stéréotaxiques

Cancer de la prostate

Cours de la SFJRO

Nancy, 10 Mars 2017

Dr D. PASQUIER

Département Universitaire de Radiothérapie, Centre O. Lambret

CRISTAL UMR CNRS 9189

Liens d’intérêts

Astellas
Ipsen
Janssen

INCA

Rationnel

Données actuelles

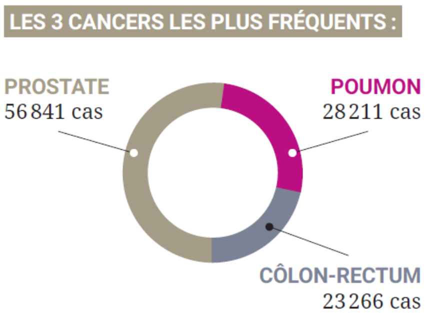
- Séries prospectives
- Essais randomisés

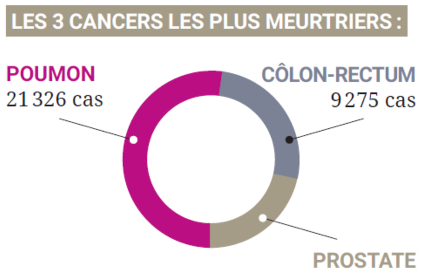
Essais en cours – à venir

Autres situations: boost, rattrapage ?

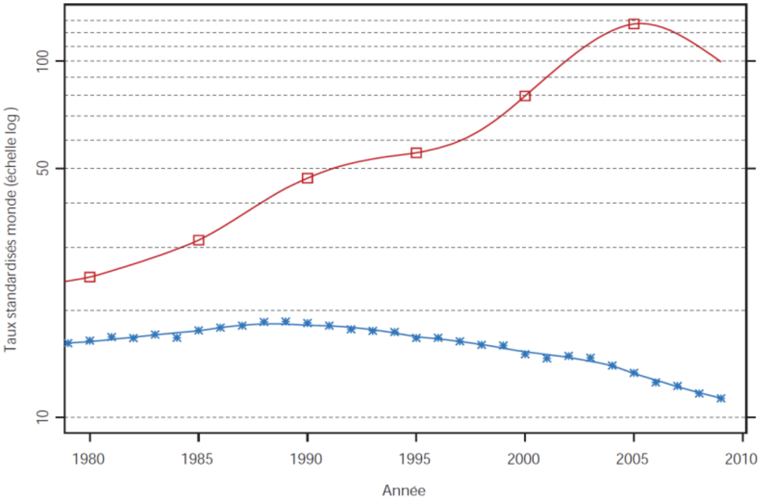
Conclusion

1er cancer chez l'homme
3ème en terme de mortalité





INCA 2014

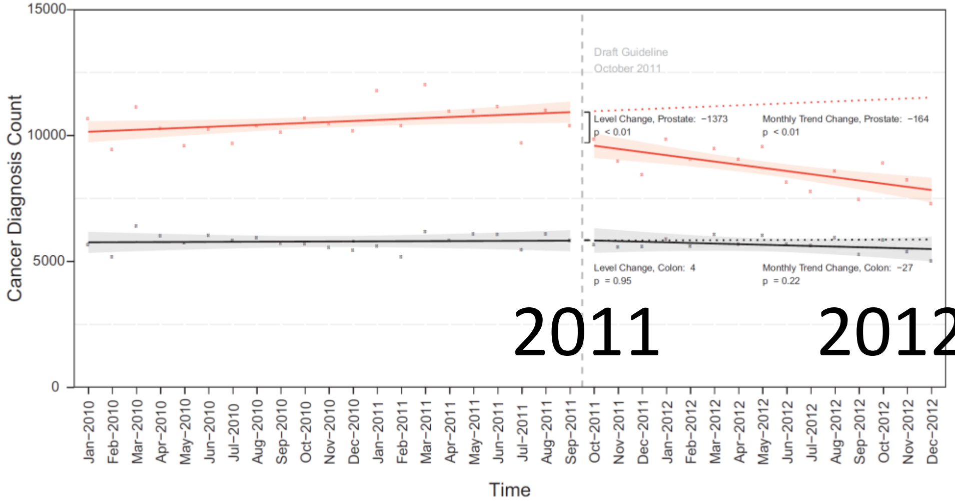


Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States

2016

www.jurology.com

Daniel A. Barocas,*,† Katherine Mallin, Amy J. Graves, David F. Penson,



2011 2012

- 28 %

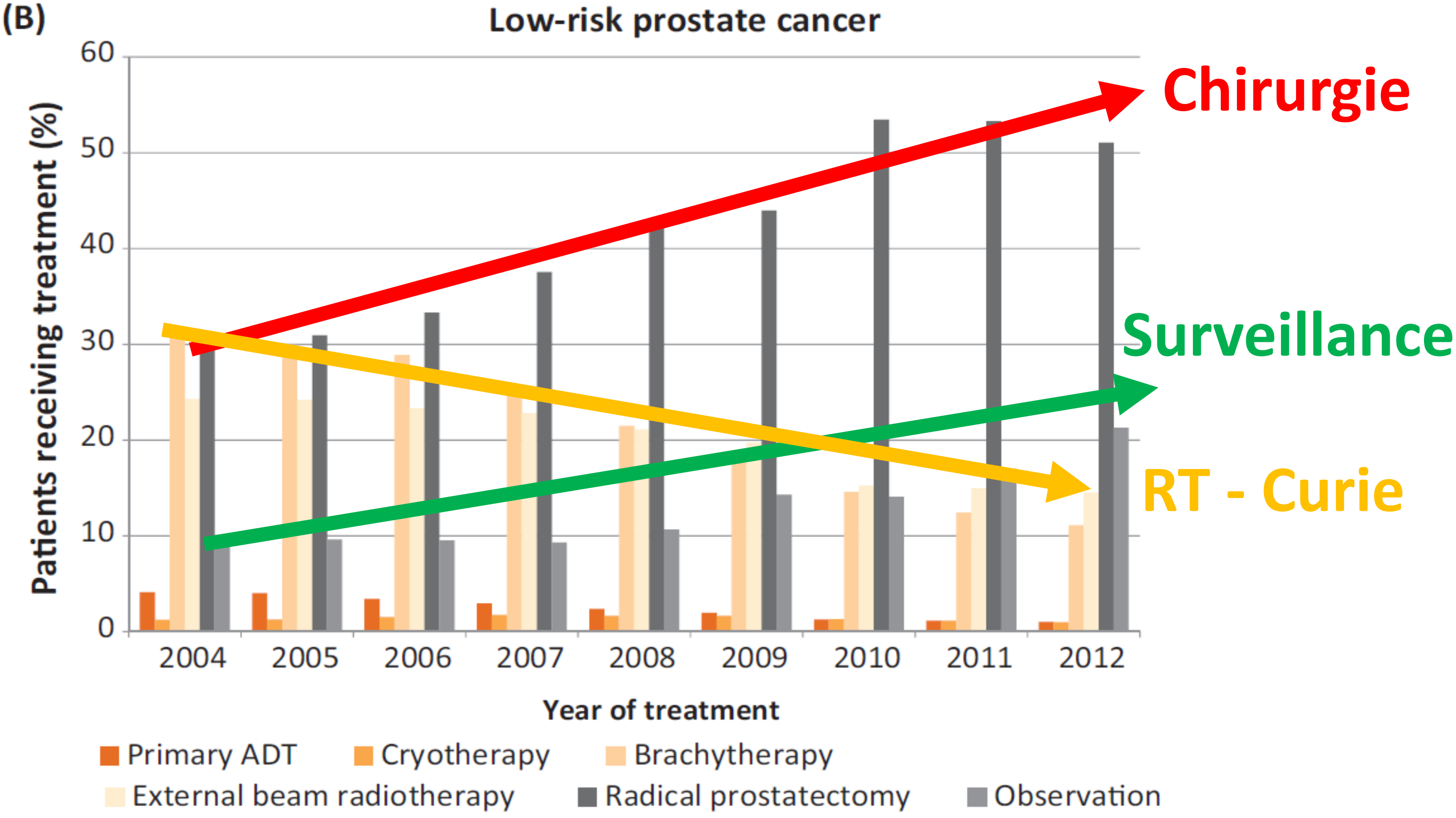
(F.R. - 38 %)

Temporal Trends and the Impact of Race, Insurance, and Socioeconomic Status in the Management of Localized Prostate Cancer

2016

Phillip J. Gray [a,†,*], *Chun Chieh Lin* [b,†], *Matthew R. Cooperberg* [c], *Ahmedin Jemal* [b,‡],

EUROPEAN UROLOGY
2014 Impact Factor 13.938



Chirurgie

Surveillance

RT - Curie

Temporal Trends and the Impact of Race, Insurance, and Socioeconomic Status in the Management of Localized Prostate Cancer

2016

Phillip J. Gray [a,†,*], *Chun Chieh Lin* [b,†], *Matthew R. Cooperberg* [c], *Ahmedin Jemal* [b,‡],

EUROPEAN
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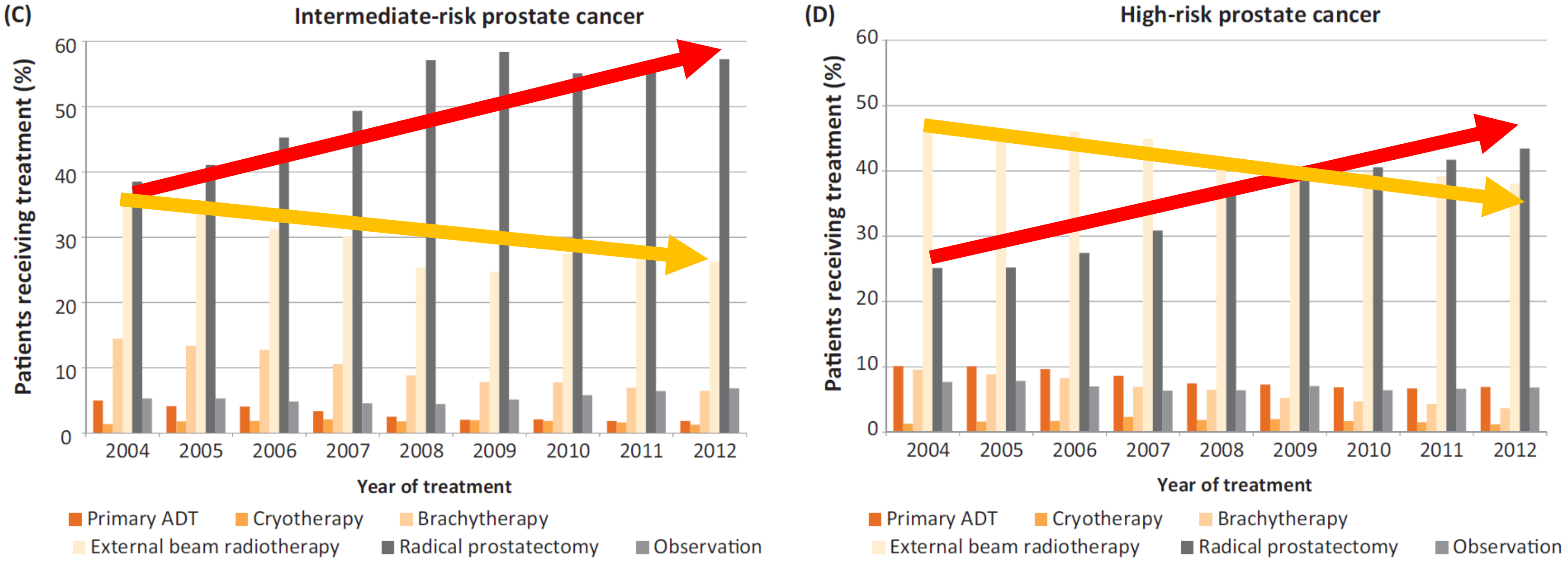
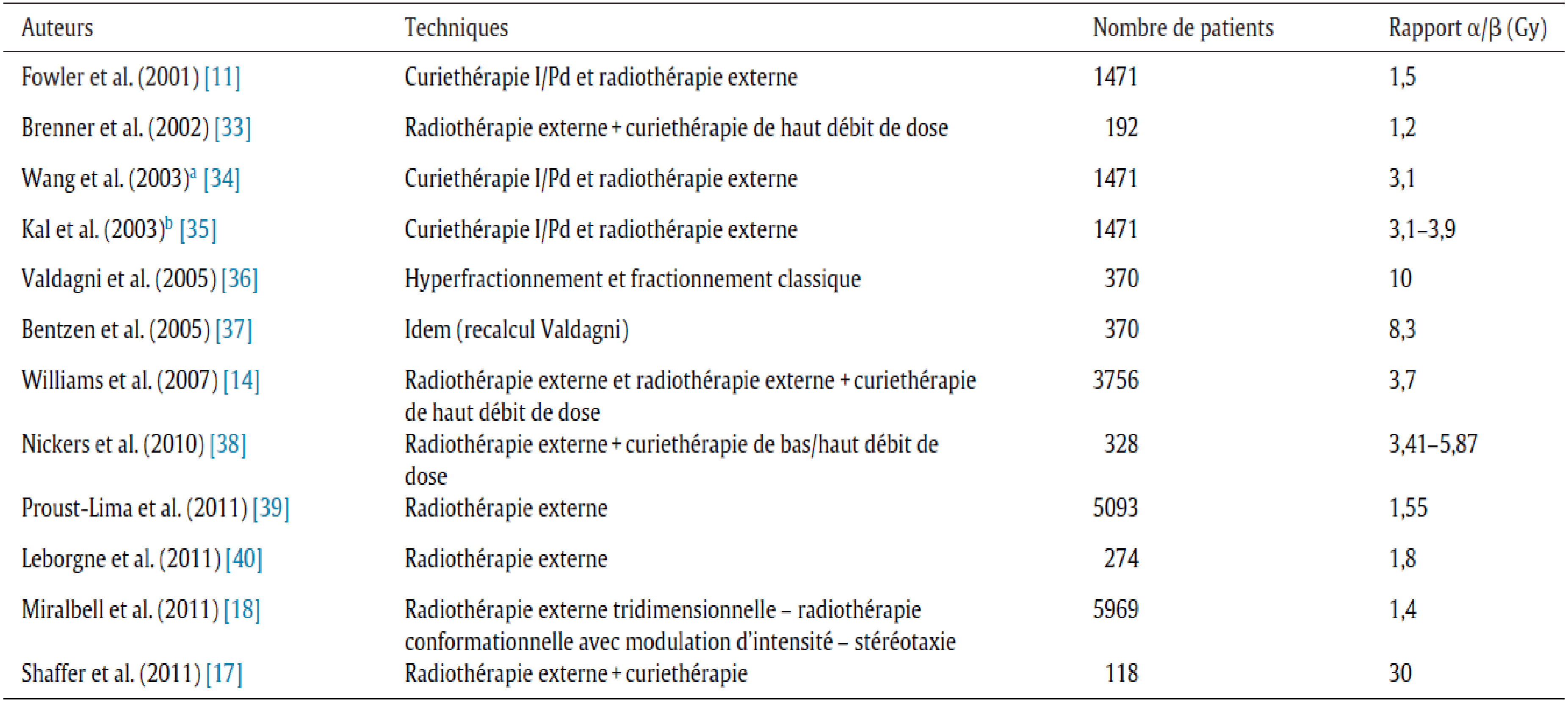


Rationnel
Hypofractionnement

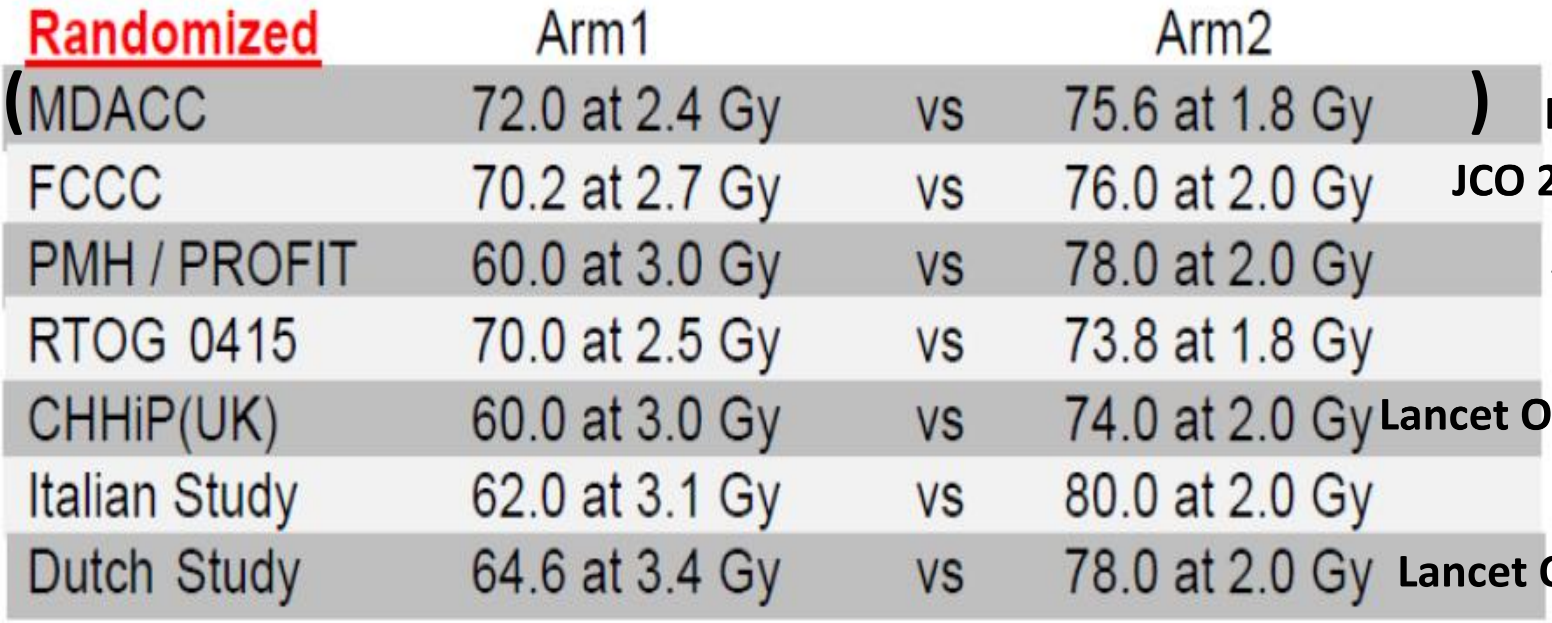
α/β du cancer de la prostate…



Auteurs	Techniques	Nombre de patients	Rapport α/β (Gy)
Fowler et al. (2001) [11]	Curiethérapie I/Pd et radiothérapie externe	1471	1,5
Brenner et al. (2002) [33]	Radiothérapie externe + curiethérapie de haut débit de dose	192	1,2
Wang et al. (2003)[a] [34]	Curiethérapie I/Pd et radiothérapie externe	1471	3,1
Kal et al. (2003)[b] [35]	Curiethérapie I/Pd et radiothérapie externe	1471	3,1–3,9
Valdagni et al. (2005) [36]	Hyperfractionnement et fractionnement classique	370	10
Bentzen et al. (2005) [37]	Idem (recalcul Valdagni)	370	8,3
Williams et al. (2007) [14]	Radiothérapie externe et radiothérapie externe + curiethérapie de haut débit de dose	3756	3,7
Nickers et al. (2010) [38]	Radiothérapie externe + curiethérapie de bas/haut débit de dose	328	3,41–5,87
Proust-Lima et al. (2011) [39]	Radiothérapie externe	5093	1,55
Leborgne et al. (2011) [40]	Radiothérapie externe	274	1,8
Miralbell et al. (2011) [18]	Radiothérapie externe tridimensionnelle – radiothérapie conformationnelle avec modulation d'intensité – stéréotaxie	5969	1,4
Shaffer et al. (2011) [17]	Radiothérapie externe + curiethérapie	118	30

Hennequin Cancer Radiother 2013

Hypofractionnement modéré
Essais randomisés

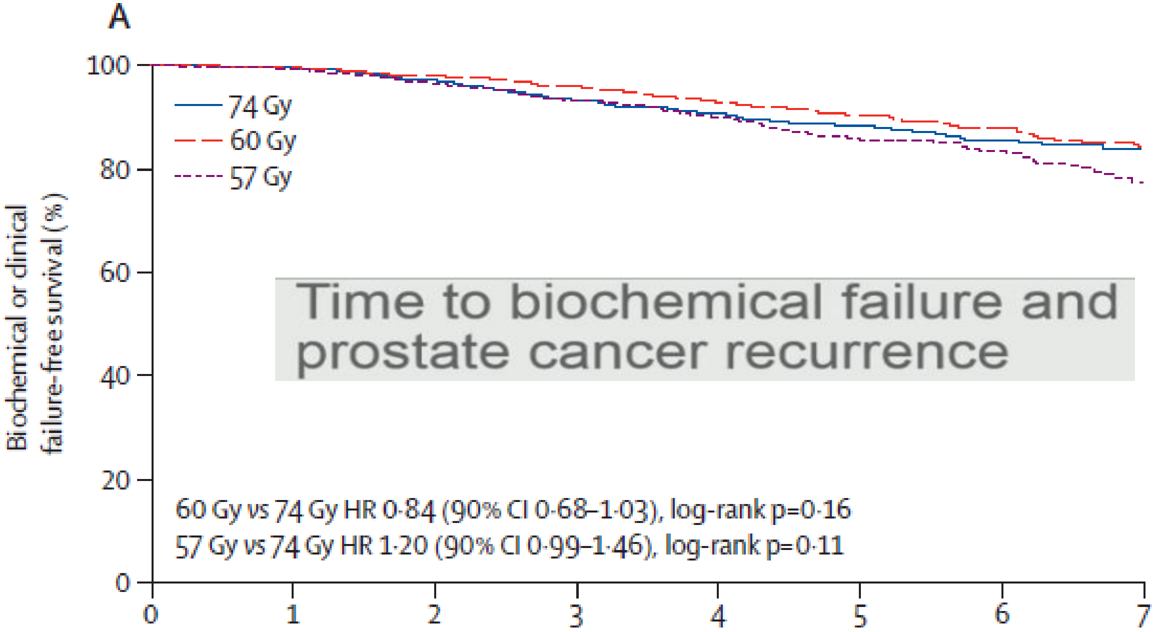


Randomized	Arm1		Arm2	
(MDACC	72.0 at 2.4 Gy	vs	75.6 at 1.8 Gy)	IJROBP 2014
FCCC	70.2 at 2.7 Gy	vs	76.0 at 2.0 Gy	JCO 2013, IJROBP 2017
PMH / PROFIT	60.0 at 3.0 Gy	vs	78.0 at 2.0 Gy	ASCO ASTRO 2016
RTOG 0415	70.0 at 2.5 Gy	vs	73.8 at 1.8 Gy	JCO 2016
CHHiP(UK)	60.0 at 3.0 Gy	vs	74.0 at 2.0 Gy	Lancet Oncol 2012, 2016
Italian Study	62.0 at 3.1 Gy	vs	80.0 at 2.0 Gy	IJROBP 2016
Dutch Study	64.6 at 3.4 Gy	vs	78.0 at 2.0 Gy	Lancet Oncol 2015, 2016

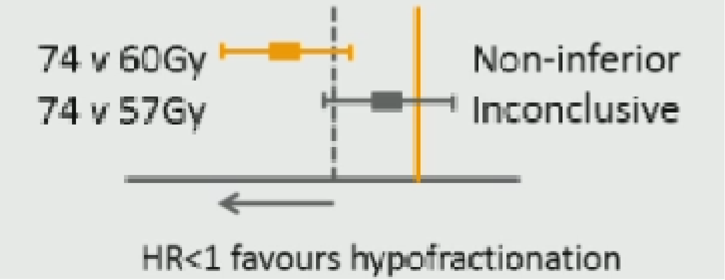
Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

Lancet Oncol 2016; 17: 1047–60

David Dearnaley, Isabel Syndikus, Helen Mossop, Vincent Khoo, Alison Birtle, David Bloomfield, John Graham, Peter Kirkbride, John Logue, Zafar Malik, Julian Money-Kyrle, Joe M O'Sullivan, Miguel Panades, Chris Parker, Helen Patterson, Christopher Scrase, John Staffurth,*



Time to biochemical failure and prostate cancer recurrence



α/β 2.5 1.5

20x3 Gy 19x3 Gy

Hazard ratio (90% CI)		0.83 (0.68, 1.02)	1.19 (0.99, 1.44)
Pr(HR<1.208)		p=0.003	p=0.91

Meta-analysis of the Alpha/Beta Ratio for Prostate Cancer in the Presence of an Overall Time Factor: Bad News, Good News, or No News?

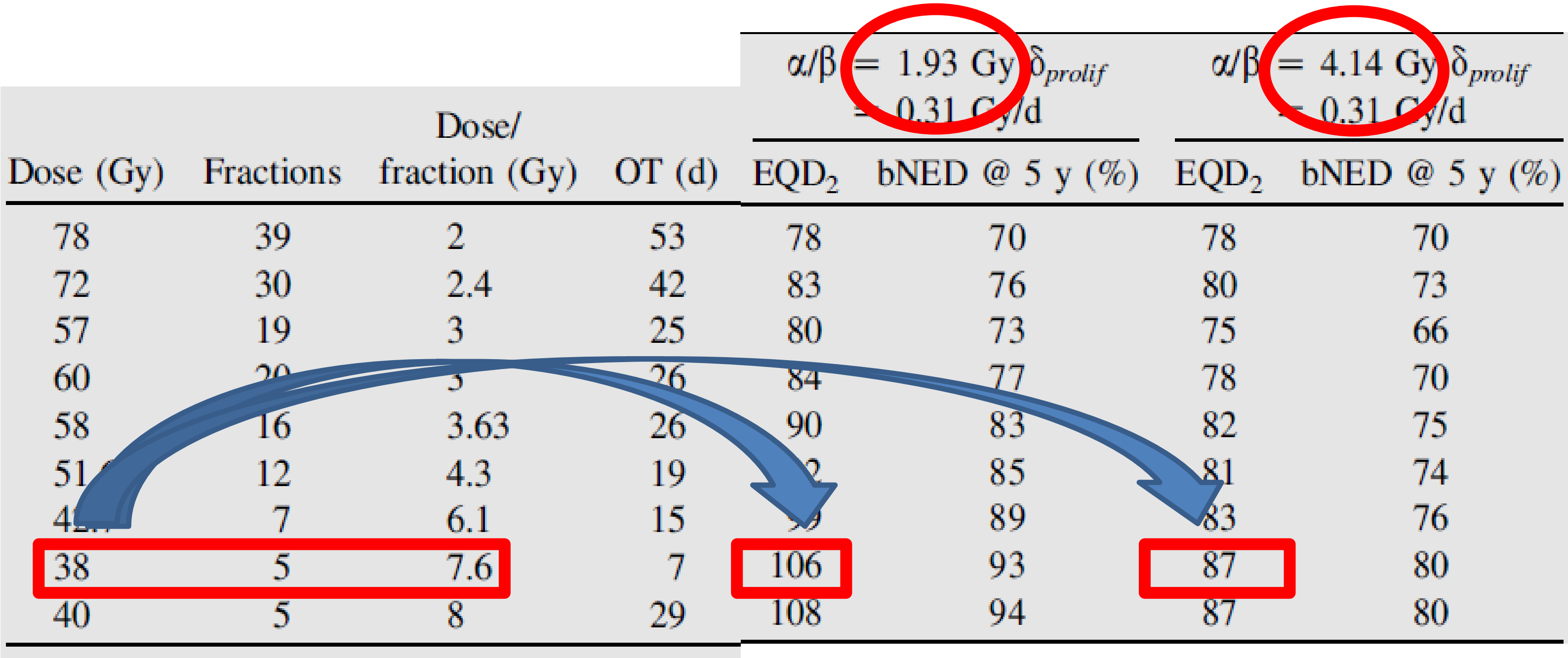
Vol. 85, No. 1, pp. 89–94, 2013

Ivan R. Vogelius, PhD,* and Søren M. Bentzen, PhD, DSc†

www.redjournal.org

# 2000 patients

➡ **1.93 Gy (IC 95 %: 0.27 – 4.14)**



				α/β = 1.93 Gy δ_{prolif} = 0.31 Gy/d		α/β = 4.14 Gy δ_{prolif} = 0.31 Gy/d	
Dose (Gy)	Fractions	Dose/ fraction (Gy)	OT (d)	EQD_2	bNED @ 5 y (%)	EQD_2	bNED @ 5 y (%)
78	39	2	53	78	70	78	70
72	30	2.4	42	83	76	80	73
57	19	3	25	80	73	75	66
60	20	3	26	84	77	78	70
58	16	3.63	26	90	83	82	75
51.6	12	4.3	19	92	85	81	74
42.7	7	6.1	15	99	89	83	76
38	5	7.6	7	106	93	87	80
40	5	8	29	108	94	87	80

Données actuelles

CLINICAL INVESTIGATION **Prostate**

STEREOTACTIC HYPOFRACTIONATED ACCURATE RADIOTHERAPY OF THE PROSTATE (SHARP), 33.5 GY IN FIVE FRACTIONS FOR LOCALIZED DISEASE: FIRST CLINICAL TRIAL RESULTS

IJROBP 2007

BERIT L. MADSEN, M.D.,* R. ALEX HSI, M.D.,* HUONG T. PHAM, M.D.,*

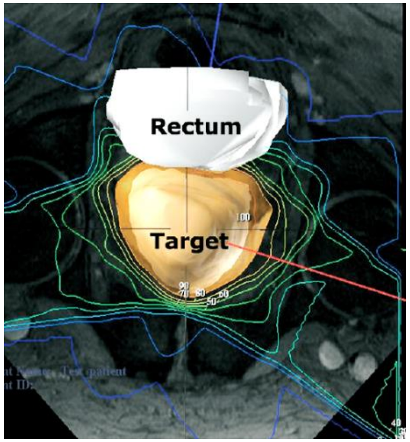
Phase I/II 2000-2004

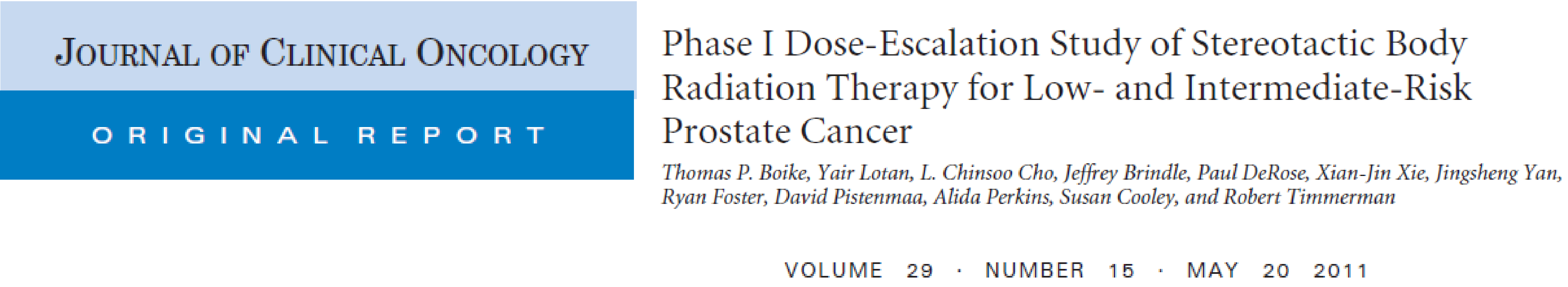
40 patients (cancer faible risque)

Procubitus
Fiduciels – IGRT quotidienne
5 x 6.7 Gy

Suivi médian 41 mois
SSRb 4 ans 90 % (Phoenix)

"Escalade de dose possible ? "





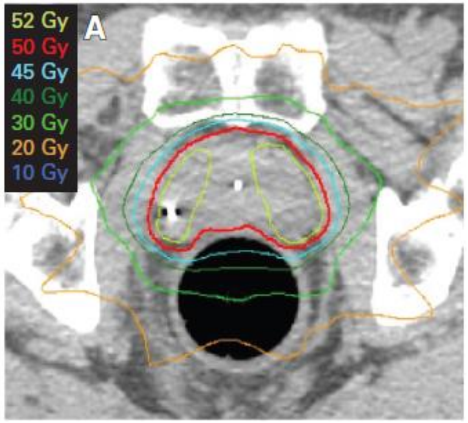
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I Dose-Escalation Study of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer

Thomas P. Boike, Yair Lotan, L. Chinsoo Cho, Jeffrey Brindle, Paul DeRose, Xian-Jin Xie, Jingsheng Yan, Ryan Foster, David Pistenmaa, Alida Perkins, Susan Cooley, and Robert Timmerman

VOLUME 29 · NUMBER 15 · MAY 20 2011



Phase I/II

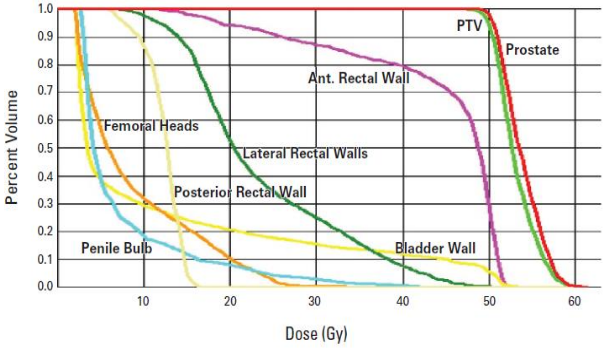
45 patients T1 – T2b

PSA < 20 ng/ml score Gleason < 6

PSA < 15 ng/ml score Gleason < 7

Volume < 60 cc IPSS < 15

	5 x 9 Gy	5 x 9.5 Gy	5 x 10 Gy
Suivi médian (mois)	**30**	**18**	**12**



Tox digestive et U: 2% et 4% grade 3

➡ **Phase II 5 x 10 Gy**

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,† Christopher Straka, BS,*

2014 www.redjournal.org

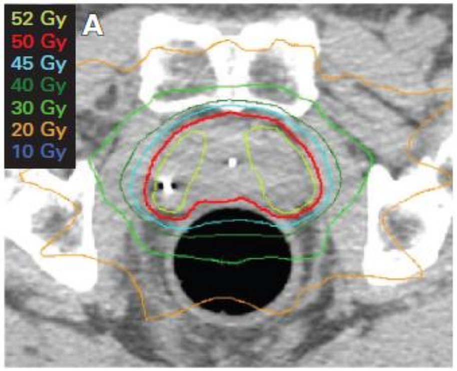
Suivi médian 25 mois **61 patients**

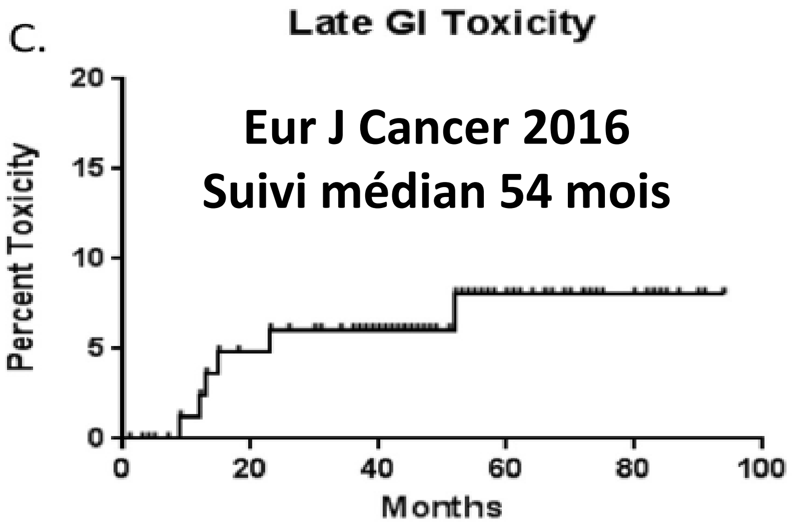
5 x 10 Gy → > 8 % toxicité digestive tardive G 3-4

☐ > 35% circonférence rectale 39 Gy

☐ > 50% 24 Gy

☐ > 3 cm3 paroi rectale 50 Gy





Eur J Cancer 2016
Suivi médian 54 mois

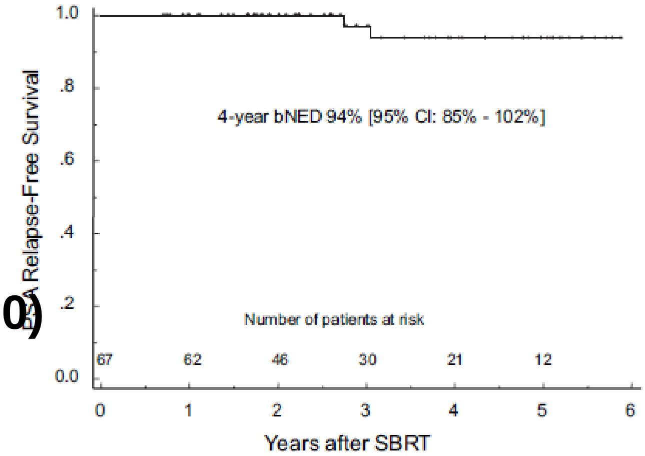
CLINICAL INVESTIGATION **Genitourinary Cancer**

LONG-TERM OUTCOMES FROM A PROSPECTIVE TRIAL OF STEREOTACTIC BODY RADIOTHERAPY FOR LOW-RISK PROSTATE CANCER

2009-2012

Christopher R. King, Ph.D., M.D.,* James D. Brooks, M.D.,† Harcharan Gill, M.D.,†

- **67 patients (FR)**
- **5 fractions de 7.25 Gy**
- **Suivi médian 33 mois**
- **SSR biochimique 4 ans 94% (IC95:85-100)**



- **"Toxicités tardives urinaire/digestive comparables RCMI "**

	GU	GI
G2	**5 %**	**2 %**
G3	**3.5 %**	**0 %**

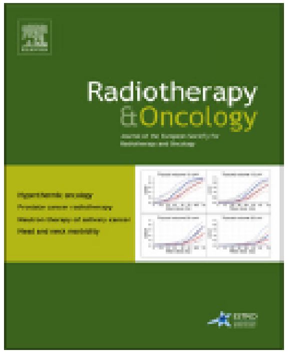
	Quotidien	1 jour/2
GU G 1-2	**56 % (9/16)**	**17 % (7/41)**
GI G 1-2	**44 % (7/16)**	**5 % (2/41)**

p = 0.001

	n	Groupe	Dose	Fr	Suivi médian	SSRb	Tox tardive G3+	
							GU	GI
Bolzicco 2013	100	BR-RI-HR	35	5	3	94.4	1%	0%
Chen 2014	100	BR-RI-HR	35–36.25	5	2.3	99.0	1%	0%
Freeman and King 2011	41	BR	35–36.25	5	5	93	2%	0%
Friedland 2009	112	BR-RI	35–36	5	2	98	0%	1%
Hannan 2016	91	BR-RI	45–50	5	4.5	98.6	5.5%	7%
Jabbari 2012	38	BR-RI	38	4	1.5	100	5%	0%
Kang 2011	44	BR-RI-HR	32–36	4	3.3	100, 100, 90.8	0%	0%
Katz 2014	477	BR-RI	35–36.25	5	7	95.6, 90	2%	0%
King 2009	41	BR	36.25	5	2.75	100	5%	0%
King 2012	67	BR	36.25	5	2.7	94.0	3%	0%
Mantz 2010	54	BR	40	5	2.2	100	0%	0%
McBride 2012	45	BR	36.25–37.5	5	3.7	97.7	2%	4%
Oliai 2012	70	BR-RI-HR	35–37.5	5	3.1	100, 95, 77.1	3%	0%

Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆,☆☆

King et al. Radiother Oncol 2013

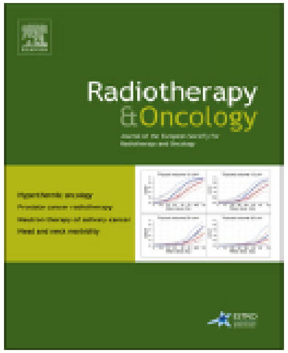

Radiotherapy &Oncology

- **1100 patients 2003 – 2011 Phases II (8 centres)**
- **58 % faible risque + 30 % risque intermédiaire + 11 % haut risque (Damico)**
- **Hormono (médiane 4 mois): 8 % FR, 15 % RI, 38 % HR**
- **5 séances 35 Gy 35 %**
  36.2 Gy 54 %
  38 – 40 Gy 11 %

90 % dose - 95 % PTV

Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆,☆☆

King et al. Radiother Oncol 2013

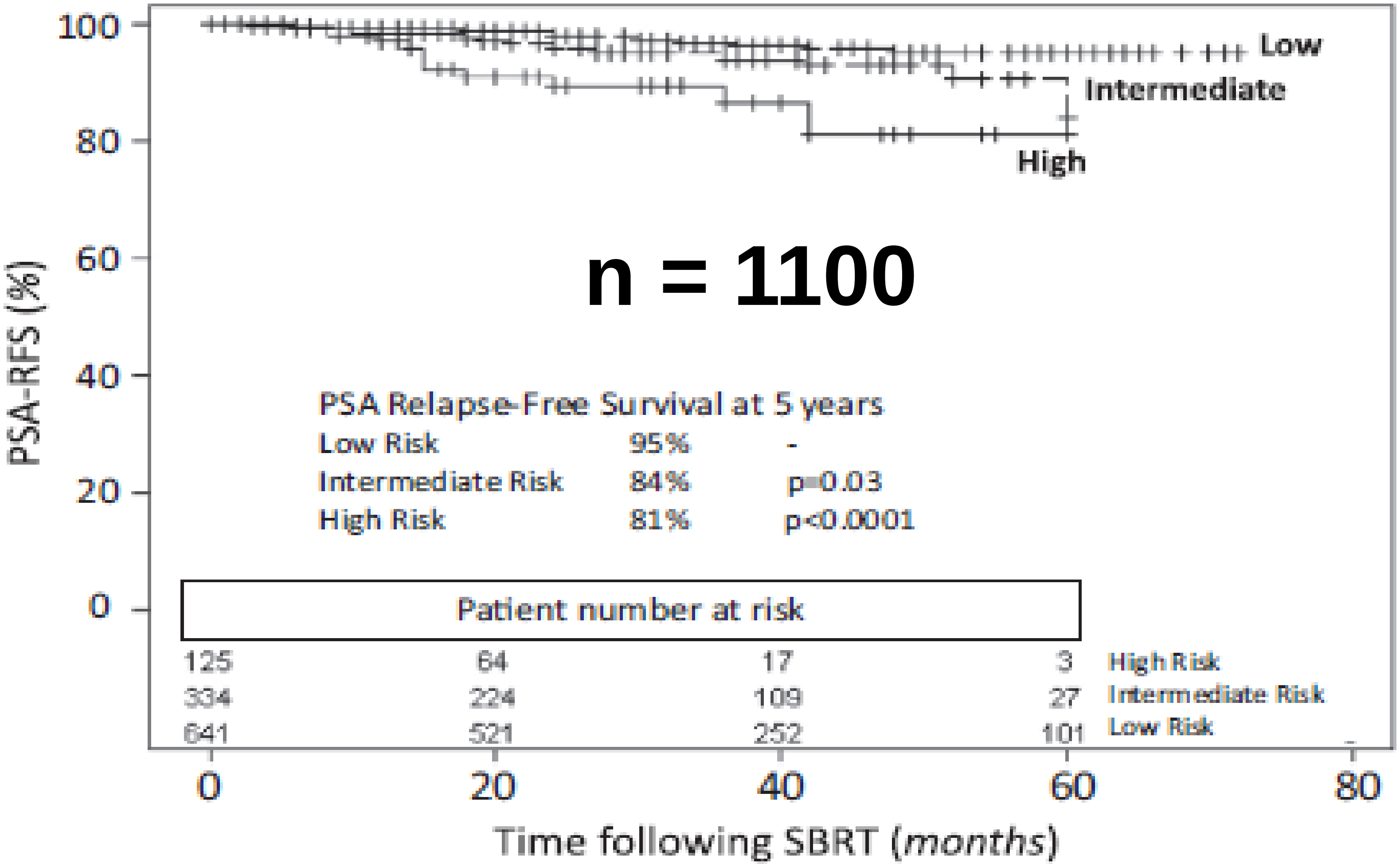


Suivi médian 36 mois

- **SSR bioch. à 5 ans 93 %**

95 % FR
84 % RI
81 % HR (p<0.001)

95 % Gleason ≤ 6
83 % 7
78 % ≥ 8
(p=0.001)



n = 1100

PSA Relapse-Free Survival at 5 years

Low Risk	95%	-
Intermediate Risk	84%	p=0.03
High Risk	81%	p<0.0001

Patient number at risk

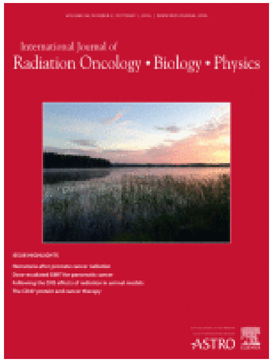
0	20	40	60	
125	64	17	3	High Risk
334	224	109	27	Intermediate Risk
641	521	252	101	Low Risk

	SSR bioch 5 ans
N = 104 FR	99 %
N = 31 RI	93 % p = 0.11

135 patients suivis > 5 ans
(60 – 72 mois)

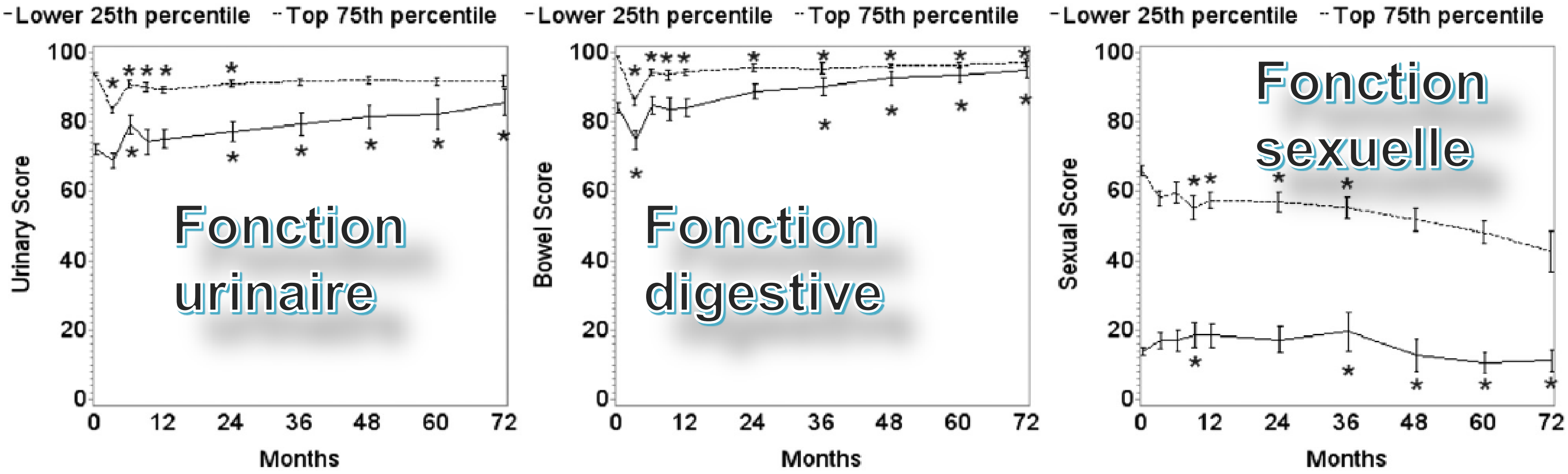
Health-Related Quality of Life After Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Results From a Multi-institutional Consortium of Prospective Trials

King et al. IJROBP 2013


International Journal of
Radiation Oncology • Biology • Physics
ASTRO

864 patients Suivi médian 36 mois

Age médian 69 ± 8 ans **Score EPIC**



Déclin 3 mois - retour normale 6 mois puis stabilité

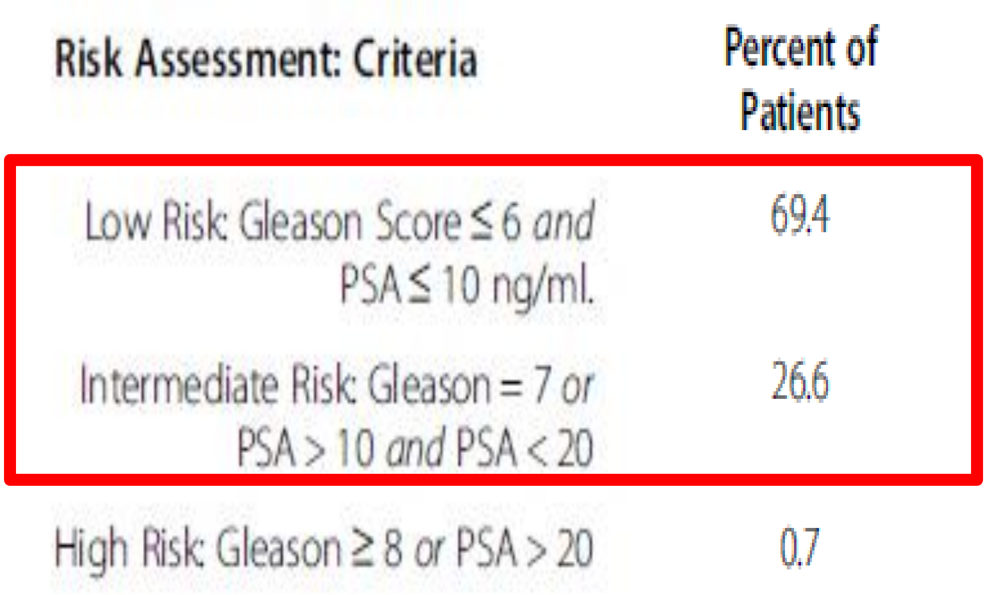
Déclin 9 mois – Stabilité – Déclin/âge

RADIATION ONCOLOGY

Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years

Katz et al. Radiat Oncol 2013

- **304 patients**
- **96% FR et RI**
- **PSA médian 5.8 ng/ml**
- **18 % HT (9% < 3 mois)**
- **5 x 7 Gy (n=50) puis 5 x 7.25 Gy**



Risk Assessment: Criteria	Percent of Patients
Low Risk: Gleason Score ≤ 6 *and* PSA ≤ 10 ng/ml.	69.4
Intermediate Risk: Gleason = 7 *or* PSA > 10 *and* PSA < 20	26.6
High Risk: Gleason ≥ 8 *or* PSA > 20	0.7

UNICANCER
Centre Oscar Lambret
Centre Régional de Lutte Contre le Cancer

RADIATION ONCOLOGY

Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years

Katz et al. Radiat Oncol 2013

- **Suivi médian 6 ans**

- **SSR bioch 97 % FR et 91 % RI**

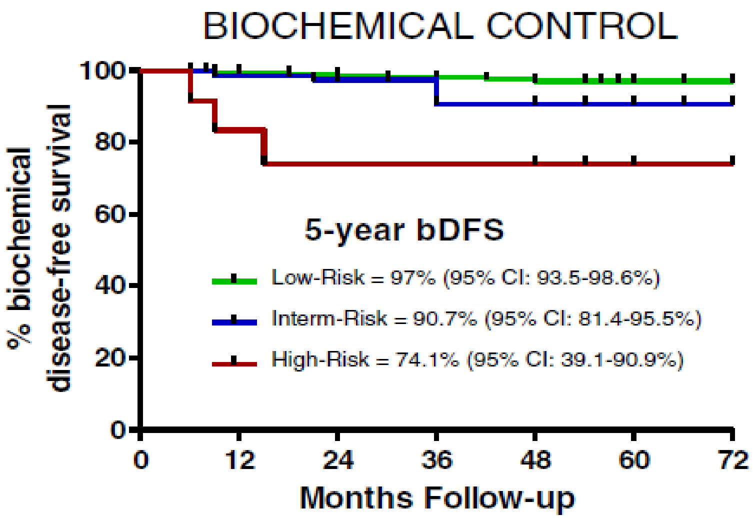
  (PSA médian 0.12 ng/ml)

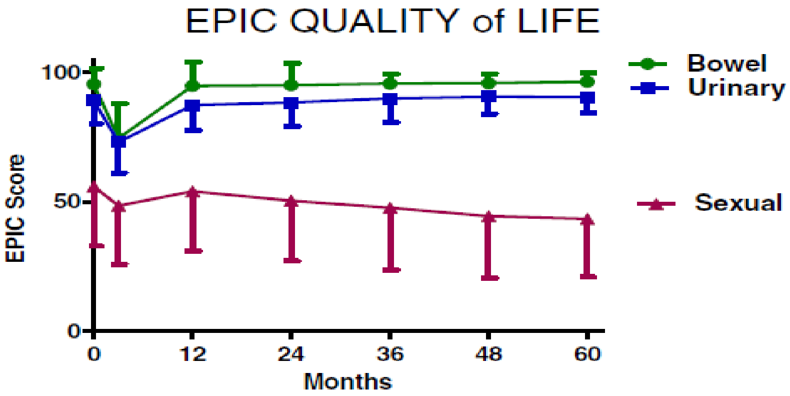
- **Tox. tardive urinaire 9 % G2**

  2 % G3

  digestive 5 % G2

- **Fonction sexuelle préservée chez 75 % des patients**





UNICANCER Centre Oscar Lambret Centre Régional de Lutte Contre le Cancer

frontiers
in Oncology

Predicting Biochemical Disease-Free Survival after Prostate Stereotactic Body Radiotherapy: Risk-Stratification and Patterns of Failure

2016

*Alan Katz[1], Silvia C. Formenti[2] and Josephine Kang[2]**

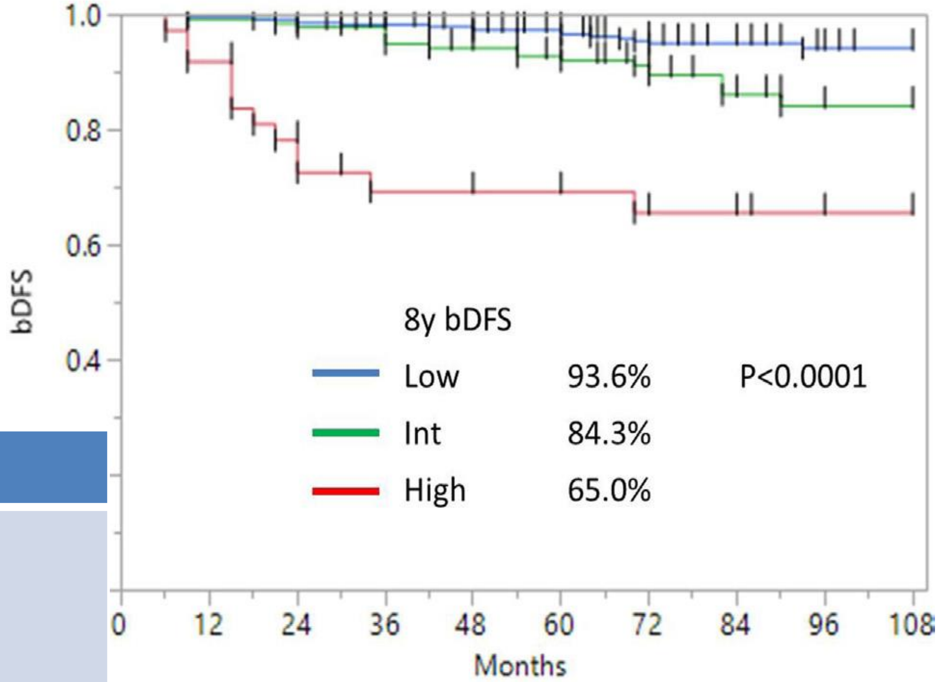
515 patients

63 % FR
30 % RI
7 % HR

SSRb à 8 ans: 94 % (IC95: 93-98) **FR**

84 % (IC95: 83-95) **RI**

	SSRb à 7 ans
RI « faible» Gleason 6 PSA > 10 Gleason 3+4 PSA < 10	93.5 % (IC95: 88-99)
RI « fort » Gleason 4+3 Gleason 3+4 PSA 10-20	79.3 % (IC95: 66-92) p=0.0036



Katz Front Oncol 2014

ASTRO **Model Policies**

Other Neoplasms Prostate Cancer:

2013 -

STEREOTACTIC BODY RADIATION THERAPY (SBRT)

It is ASTRO's opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Prostate Cancer

2014 -

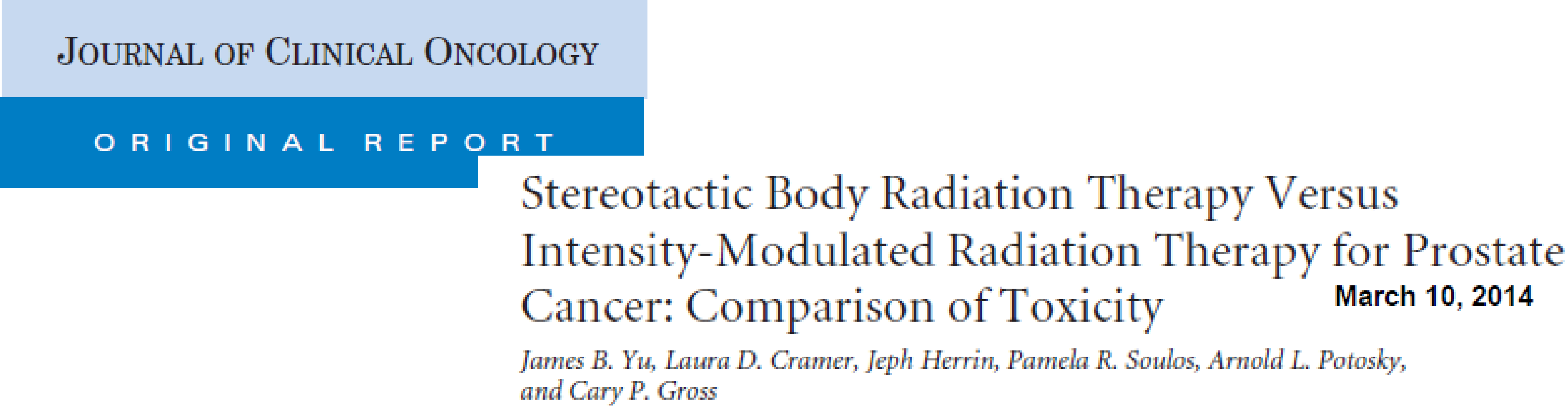
- Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.

eau European Association of Urology

RECORAD

2016 -

For extreme HFX, it seems prudent to restrict this therapy to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.



JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross

March 10, 2014

Etude *rétrospective* 2008 – 2011 Medicare Age > 66 ans

1300 SBRT appariés 2600 RCMI suivis 6, 12 et 24 mois

Etude coût et toxicité; codification *actes médicaux (débitmétrie) # toxicité*

SBRT patients plus jeunes, moins de co-morbidités, HT moins fréquente

11 vs 42 %

Cout SBRT 13000 $ < RCMI 21000 $

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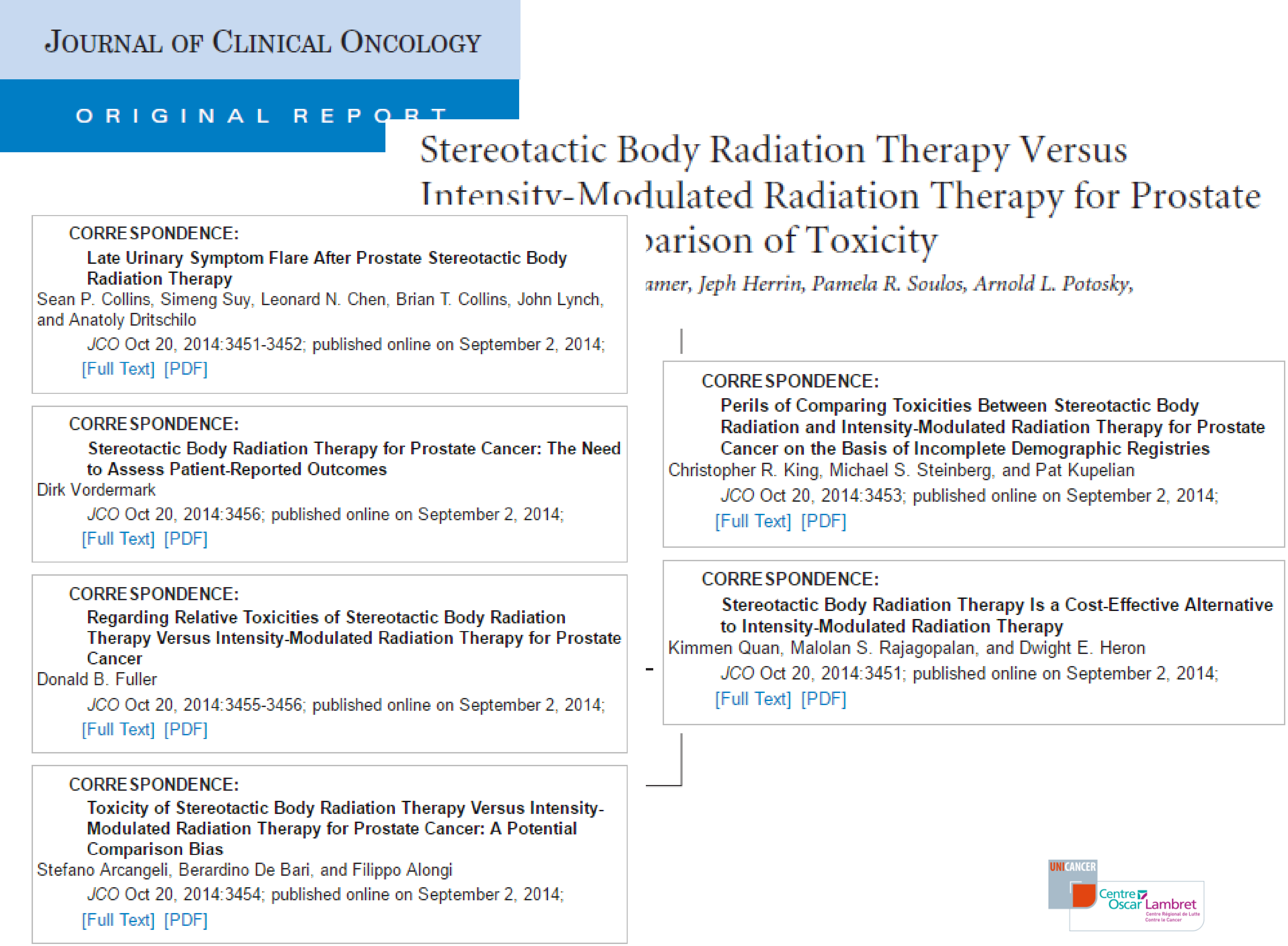
Centre Régional de Lutte Contre le Cancer



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ORIGINAL REPORT

Stereotactic Body Radiation Therapy Versus
Intensity-Modulated Radiation Therapy for Prostate
parison of Toxicity

amer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky,

CORRESPONDENCE:

Late Urinary Symptom Flare After Prostate Stereotactic Body Radiation Therapy

Sean P. Collins, Simeng Suy, Leonard N. Chen, Brian T. Collins, John Lynch, and Anatoly Dritschilo

JCO Oct 20, 2014:3451-3452; published online on September 2, 2014;

[Full Text] [PDF]

CORRESPONDENCE:

Stereotactic Body Radiation Therapy for Prostate Cancer: The Need to Assess Patient-Reported Outcomes

Dirk Vordermark

JCO Oct 20, 2014:3456; published online on September 2, 2014;

[Full Text] [PDF]

CORRESPONDENCE:

Regarding Relative Toxicities of Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer

Donald B. Fuller

JCO Oct 20, 2014:3455-3456; published online on September 2, 2014;

[Full Text] [PDF]

CORRESPONDENCE:

Toxicity of Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: A Potential Comparison Bias

Stefano Arcangeli, Berardino De Bari, and Filippo Alongi

JCO Oct 20, 2014:3454; published online on September 2, 2014;

[Full Text] [PDF]

CORRESPONDENCE:

Perils of Comparing Toxicities Between Stereotactic Body Radiation and Intensity-Modulated Radiation Therapy for Prostate Cancer on the Basis of Incomplete Demographic Registries

Christopher R. King, Michael S. Steinberg, and Pat Kupelian

JCO Oct 20, 2014:3453; published online on September 2, 2014;

[Full Text] [PDF]

CORRESPONDENCE:

Stereotactic Body Radiation Therapy Is a Cost-Effective Alternative to Intensity-Modulated Radiation Therapy

Kimmen Quan, Malolan S. Rajagopalan, and Dwight E. Heron

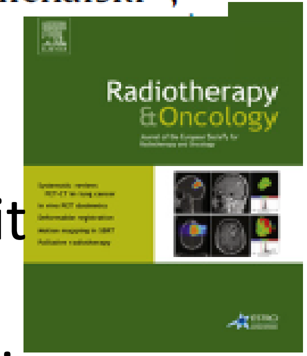
JCO Oct 20, 2014:3451; published online on September 2, 2014;

[Full Text] [PDF]

Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy

Joseph R. Evans[a,1], Shuang Zhao[a,1], Stephanie Daignault[b], Martin G. Sanda[c], Jeff Michalski[d],

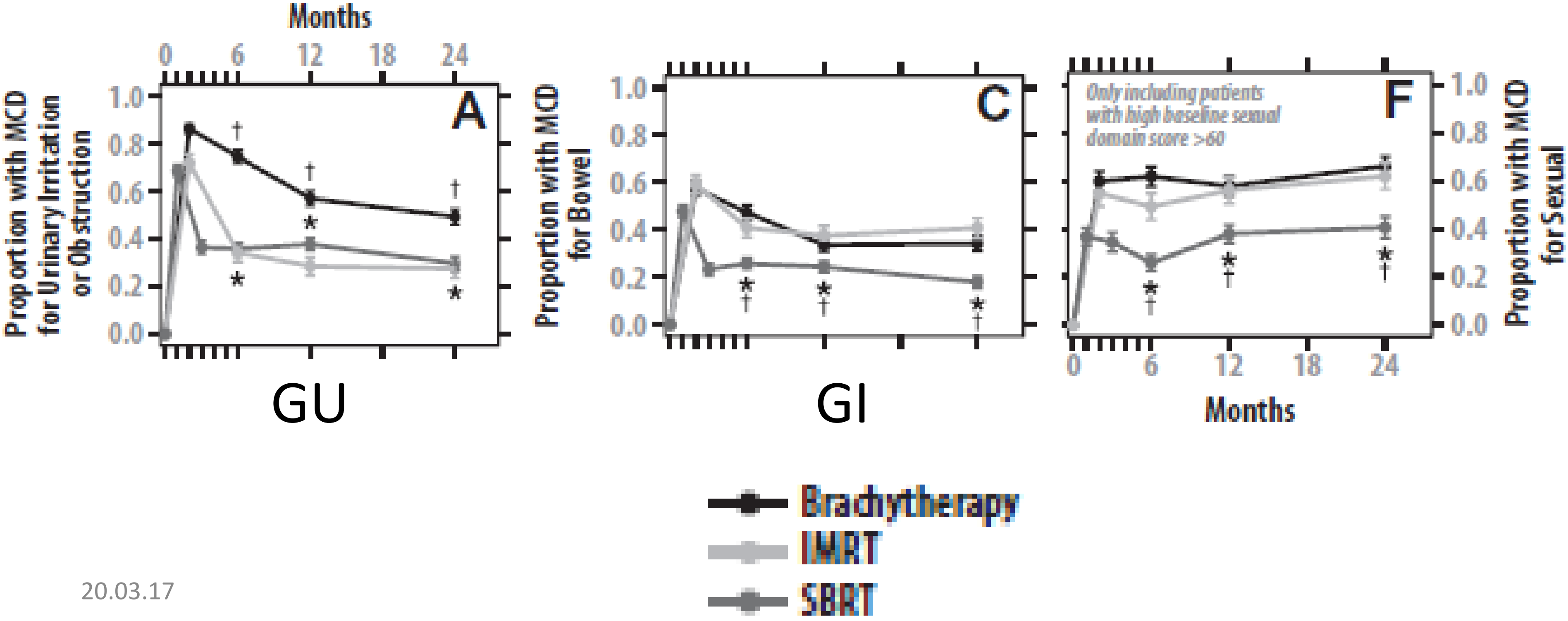
2015



803 patients FR 54 % RI 42 %

SBRT: 35-40 Gy (5fr) RCMI:75.6-79.2 Gy Curie bas débit

Evaluation *prospective* QDV (EPIC) T0, 1, 2, 6, 12 et 24 mois



GU

GI

Essais randomisés phase 3

	n	Schémas	Obj. principal
HYPO RT PC (RI)	1200	7 x 6,1 Gy vs 39 x 2 Gy	SSRb à 5 ans
PACE A-B (FR-RI)	860 (x2)	5 x 7,25 Gy vs 39 x 2 Gy	SSRb à 5 ans
NCT01794403 (FR-RI)	456	5 x 6,25 Gy vs 26 x 2,7 Gy	SSRb à 2 ans

ASTRO 2016

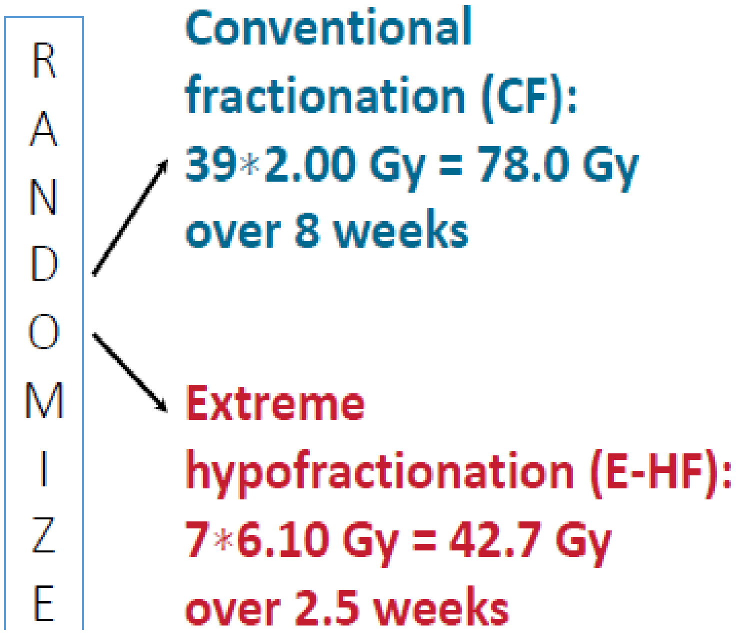
Extreme Hypofractionation vs. Conventionally Fractionated Radiotherapy for Intermediate Risk Prostate Cancer

Early Toxicity Results from the Scandinavian Randomized Phase III Trial “HYPO-RT-PC”

Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman,

Patients and Method

- Open randomized phase III trial
  - Non-inferiority design
  - 1200 patients accrued
    - July 2005-Nov 2015
  - Intermediate risk PCa
    - T1c-T3a, PSA ≤ 20, Gl ≥7, 1-2 of these risk factors were required



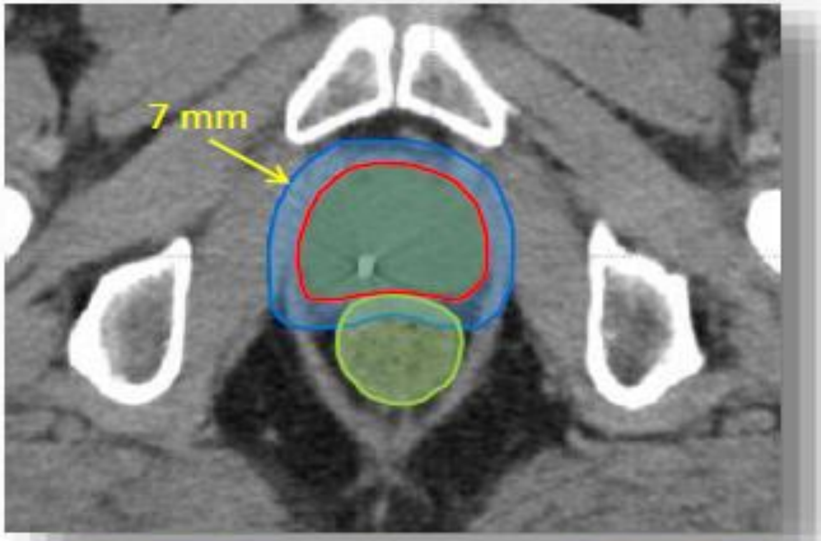
RANDOMIZE

Conventional fractionation (CF):
39*2.00 Gy = 78.0 Gy
over 8 weeks

Extreme hypofractionation (E-HF):
7*6.10 Gy = 42.7 Gy
over 2.5 weeks

Radiotherapy

- IGRT
  - based on implanted markers
- CTV=prostate
  - no seminal vesicles
- PTV=CTV + 7 mm isotropic margir
- CTV delineated on CT
  - (with MR guidance)



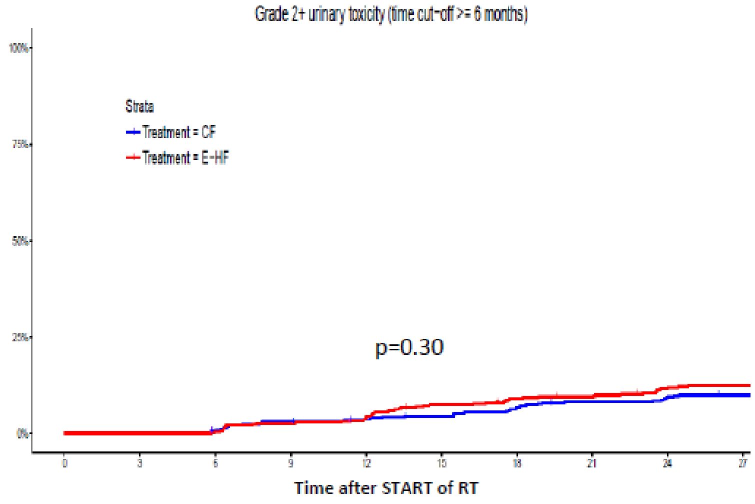
80% 3D-CRT (5-7 fields) 20% VMAT

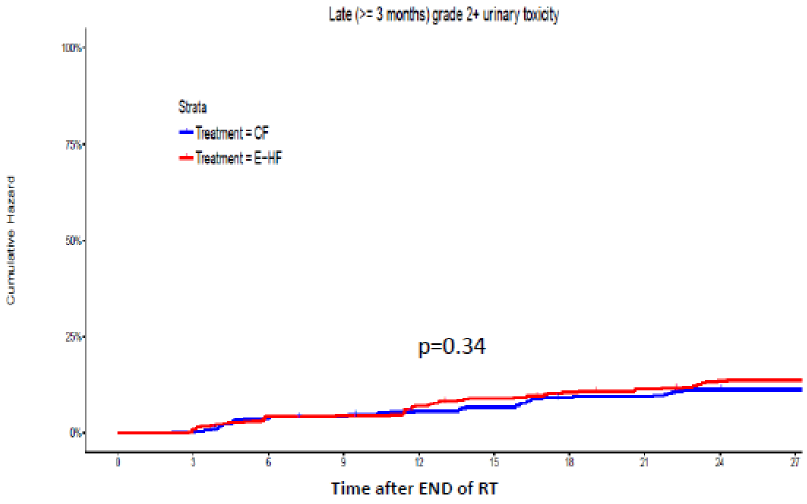
Endpoints

- Primary endpoint
  - 5 year failure free survival (FFS)
    - freedom from biochemical failure (PSA nadir + 2.0 ng/ml) or prostate cancer recurrence
- Secondary endpoints
  - PSA response rate
  - Cancer specific survival
  - Overall survival
  - Side effects and Quality of Life (QoL) (urinary, gastrointestinal morbidity and sexual function)

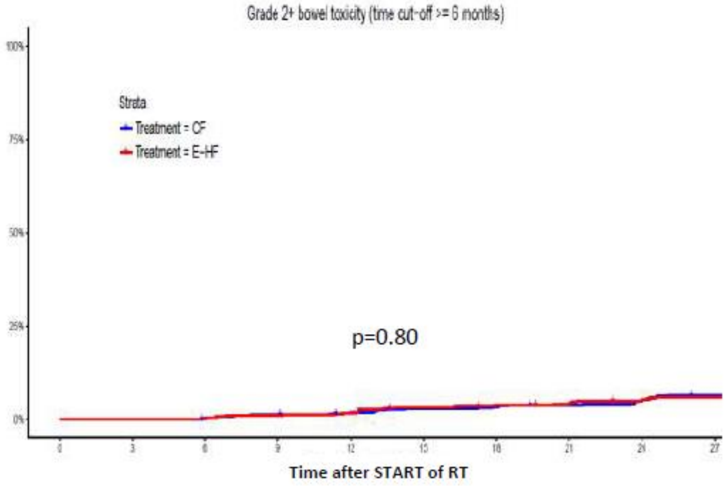
Suivi médian 2 ans

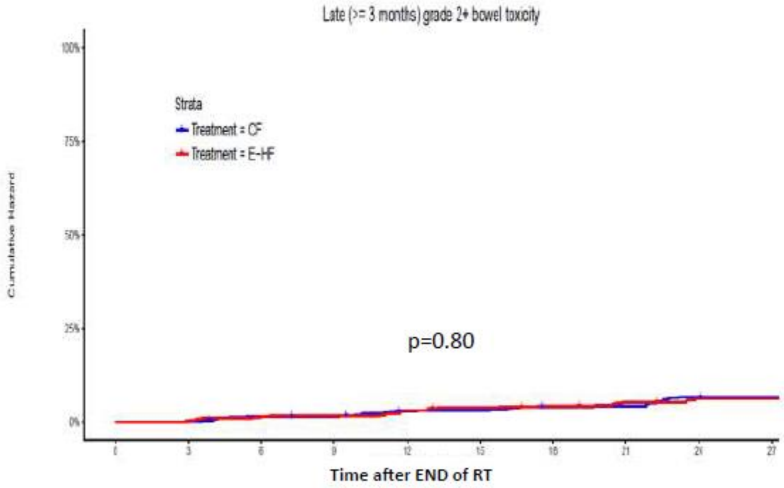
Cumulative LATE urinary toxicity ≥ Grade 2





Cumulative LATE bowel toxicity ≥ Grade 2





Essais en cours – à venir

The PACE Trial (Prostate Advances in Comparative Evidence)

Low risk
Clinical stage T1-T2a and Gleason = 6 and PSA < 10 ng/ml

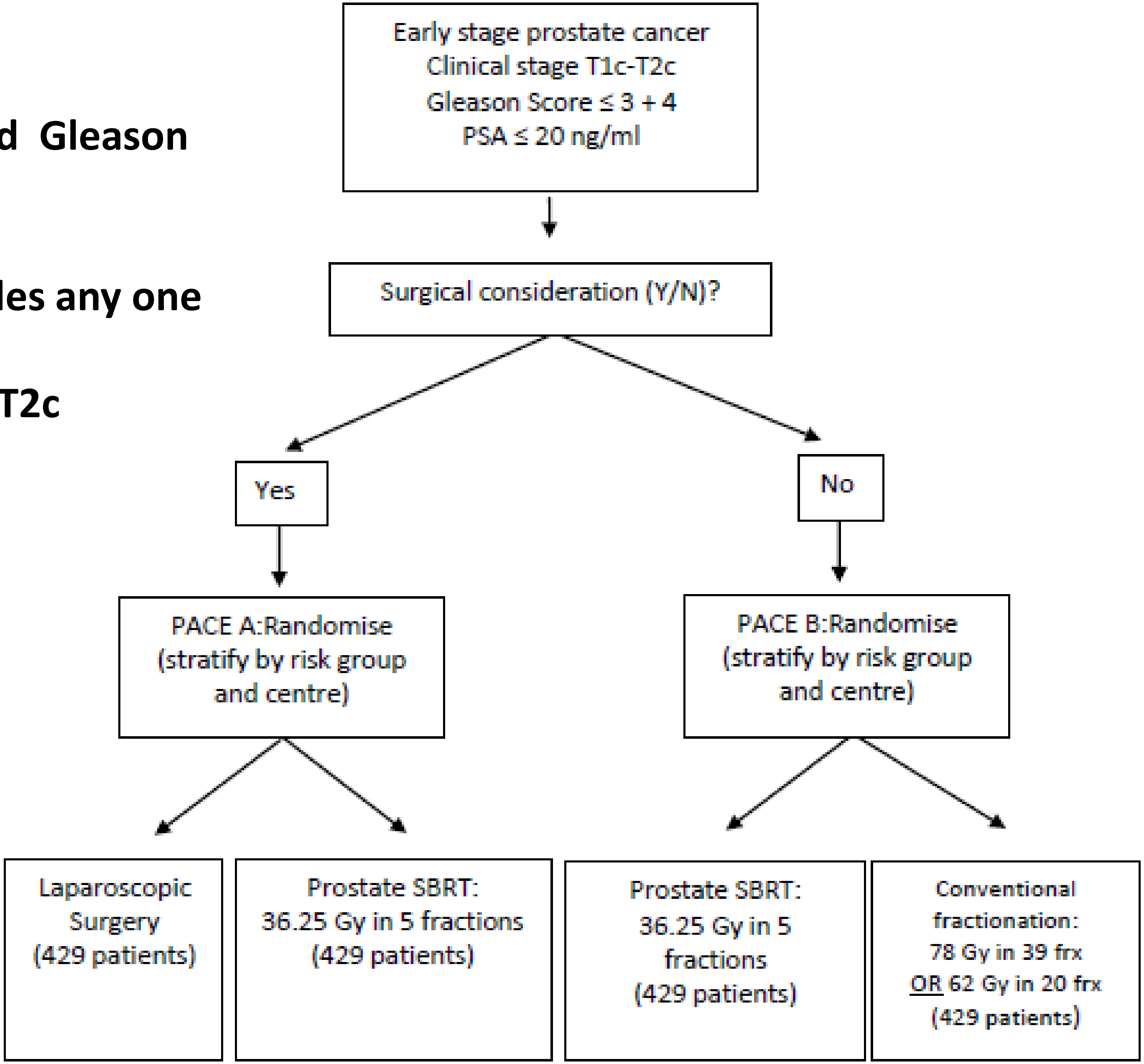
Intermediate risk includes any one of the following:

- **Clinical stage T2b orT2c**
- **PSA 10-20 ng/ml**
- **Gleason 3+4**

Non infériorité SSR

Tox, QDV…

2012 -



Early stage prostate cancer
Clinical stage T1c-T2c
Gleason Score ≤ 3 + 4
PSA ≤ 20 ng/ml

Surgical consideration (Y/N)?

Yes

No

PACE A:Randomise (stratify by risk group and centre)

PACE B:Randomise (stratify by risk group and centre)

Laparoscopic Surgery (429 patients)

Prostate SBRT: 36.25 Gy in 5 fractions (429 patients)

Prostate SBRT: 36.25 Gy in 5 fractions (429 patients)

Conventional fractionation: 78 Gy in 39 frx OR 62 Gy in 20 frx (429 patients)

frontiers in
ONCOLOGY

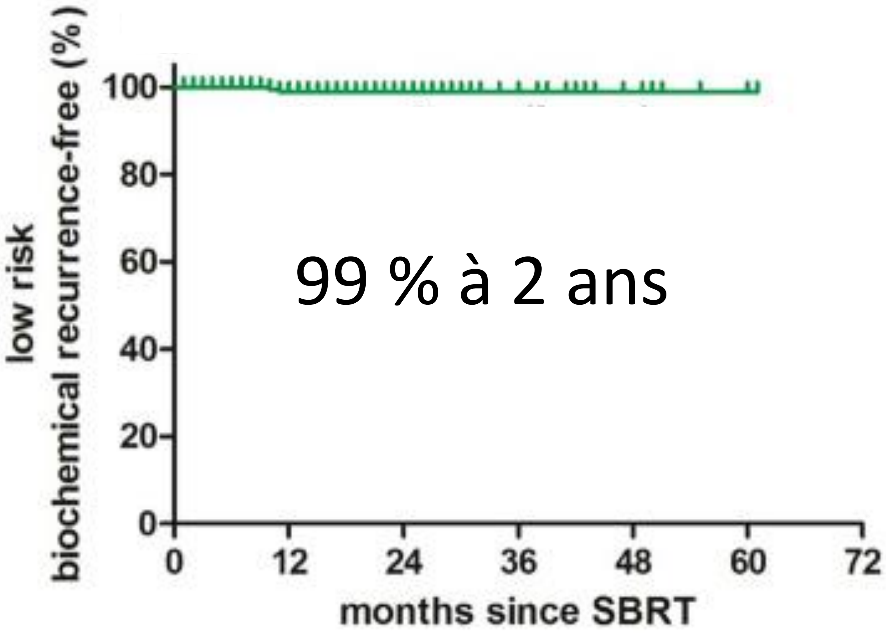
CLINICAL TRIAL ARTICLE
published: 22 January 2015
doi: 10.3389/fonc.2014.00369

Multi-institutional registry for prostate cancer radiosurgery: a prospective observational clinical trial

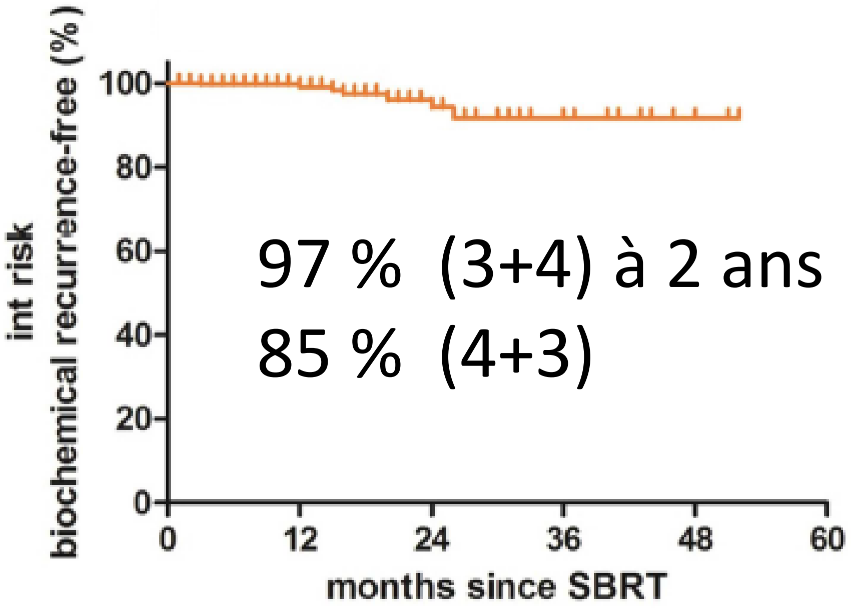
Debra Freeman[1*], *Gregg Dickerson*[2] *and Mark Perman*[2]

2010-2013 ♯ 2000/2700 patients

FR 41 % RI 42 %

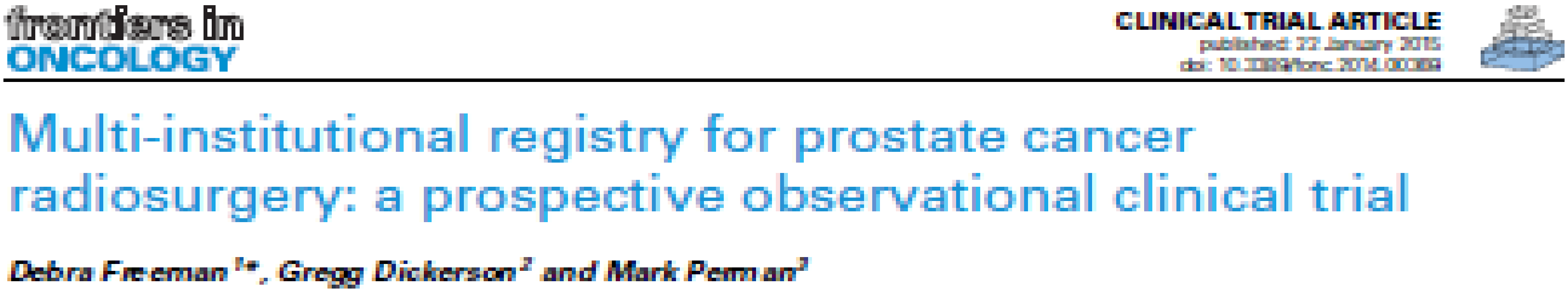


99 % à 2 ans



97 % (3+4) à 2 ans

85 % (4+3)



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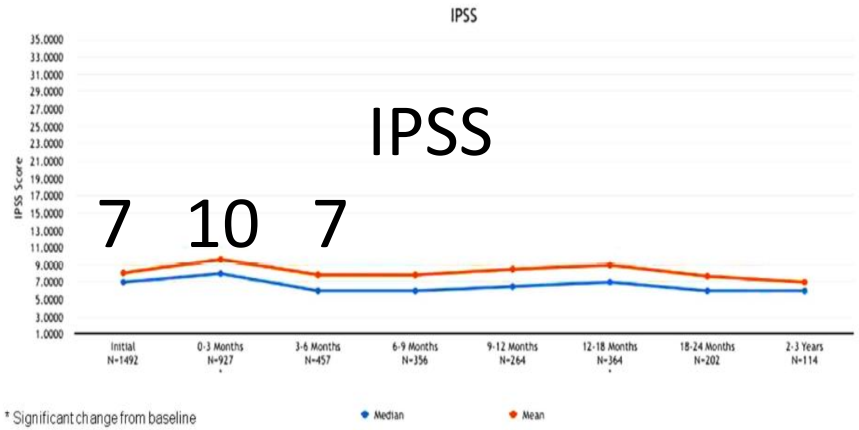


IPSS

7 10 7

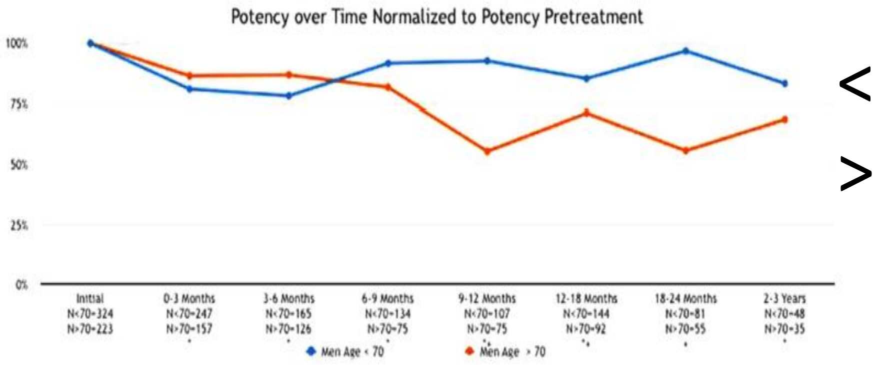
* Significant change from baseline

10 % SFU « modérés »

0 G3

1 tox digestive G3

Potency(IIEF-5 Question 2 score ≥ 3)



< 70 ans: 80 %

> 70 ans: 55 %

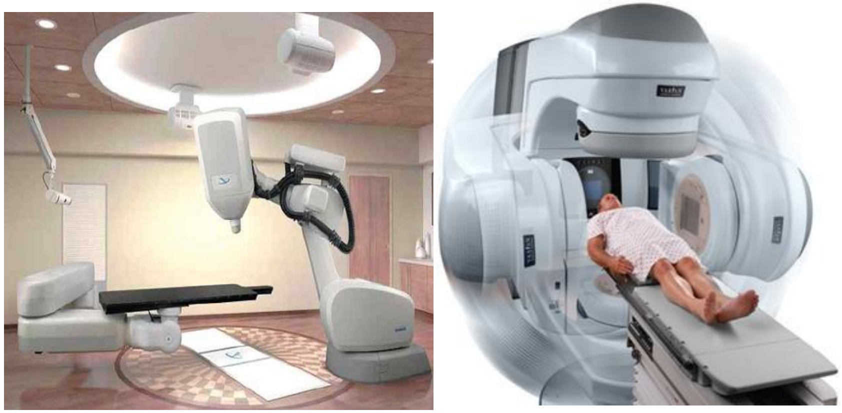
* Significant change from Initial for Men Age < 70

+ Significant change from Initial for Men Age > 70

Autres situations

Boost stéréo
Phase II multicentrique CKNO PRO

PHRC-K 2009
Lille - Nancy- Dijon - Lyon



RT3D 46Gy en 23 x 2Gy **puis 3 x 6 Gy**

76 patients RI (2010-2013)
57/76 Gleason 7

PSA moyen 8.8 ng/ml (±4.2)

Suivi médian 26 mois

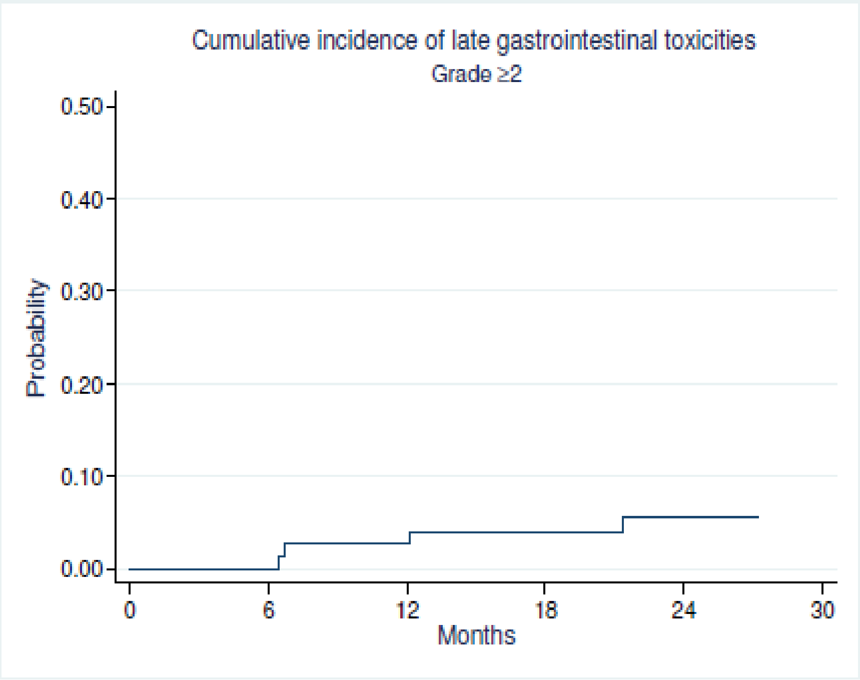
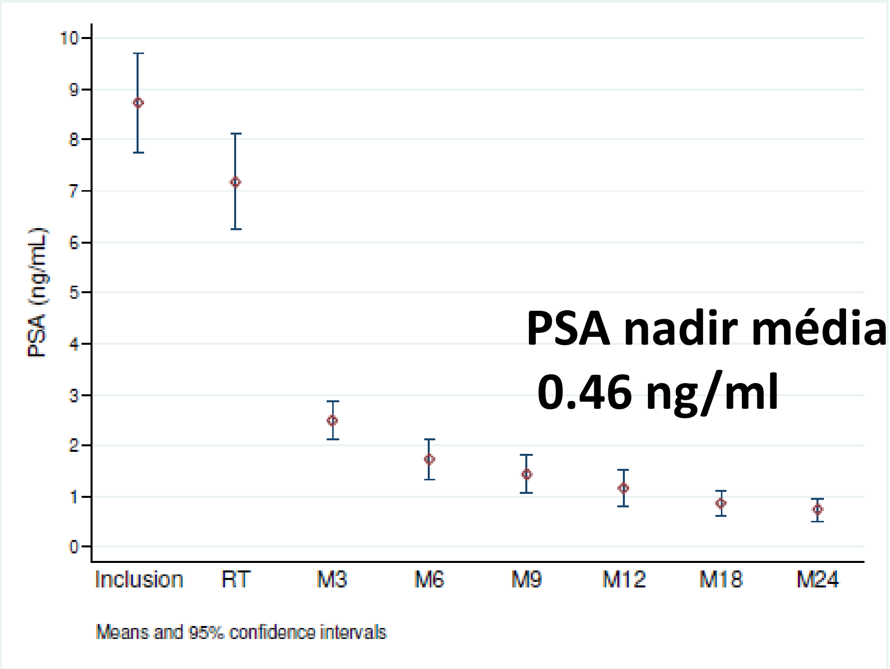


Figure 9. PSA à l'inclusion, pendant RT et pendant les suivis : moyennes et CI 95%

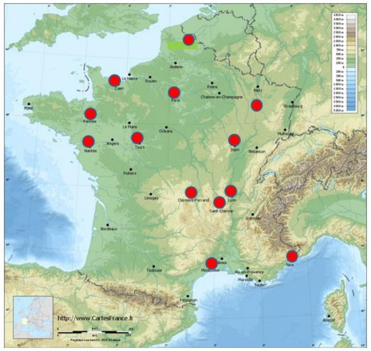


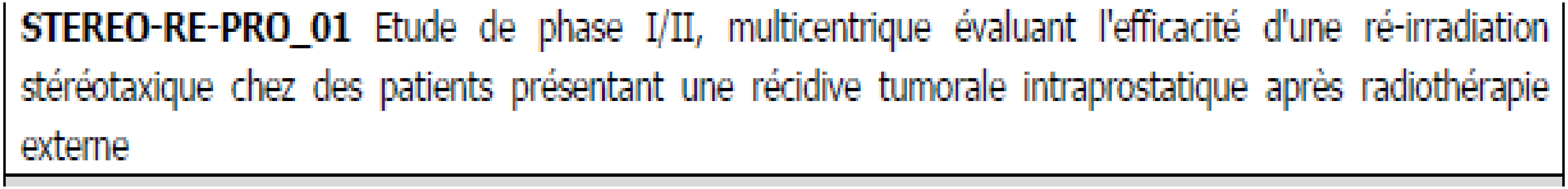
PSA nadir médian
0.46 ng/ml

Toxicité: 2.6 % (2/76) G2 GU

6.6 % (5/76) G2+ GI (dont 1 G3)

PHRC-K 2015
GETUG-AFU 31





STEREO-RE-PRO_01 Etude de phase I/II, multicentrique évaluant l'efficacité d'une ré-irradiation stéréotaxique chez des patients présentant une récidive tumorale intraprostatique après radiothérapie externe

Phase I/II: 5 x 6 Gy puis 6 x 6 Gy

N= 53

2017 -

Durée inclusion: 36 mois

Conclusion
Stéréotaxie cancer prostatique

Evolution «naturelle» de la RT prostatique ?

Toxicité rectale faible

Toxicités urinaire et sexuelle faibles (sélection des patients !)

Suivi encore court; probablement demain une option:

- **Faible risque**
- **Risque intermédiaire**

Boost pour le RI ?

UNICANCER
Centre Oscar Lambret
Centre Régional de Lutte Contre le Cancer