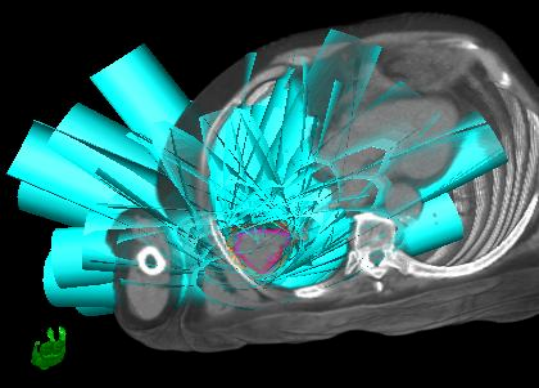
CKNO
CyberKnife® Nord Ouest

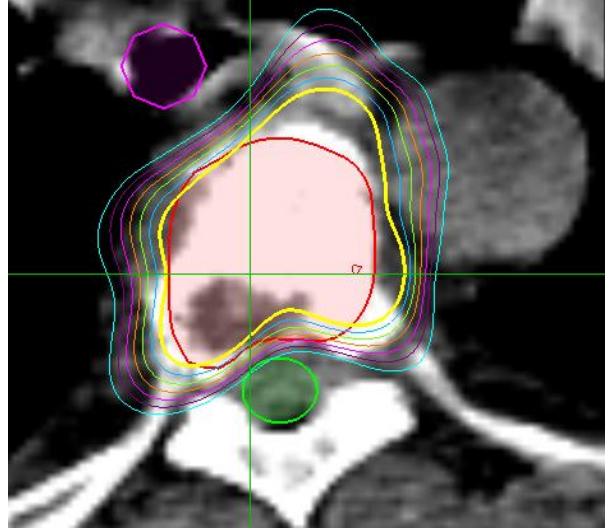
Extracranial SBRT:
from technical availabilities to clinical opportunities

Centre Oscar Lambret

Pr. Eric F. LARTIGAU
Centre Oscar Lambret, Lille
France

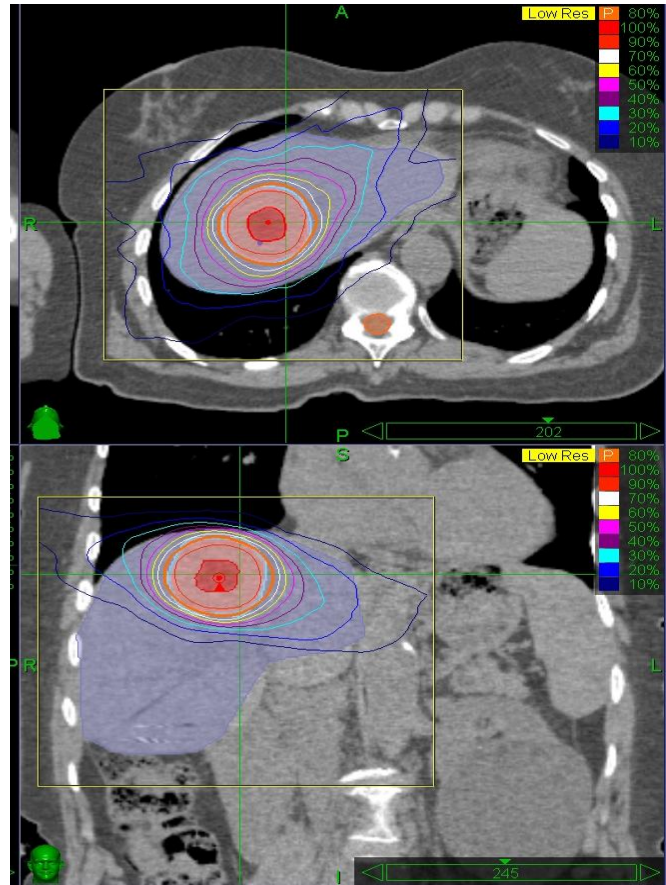


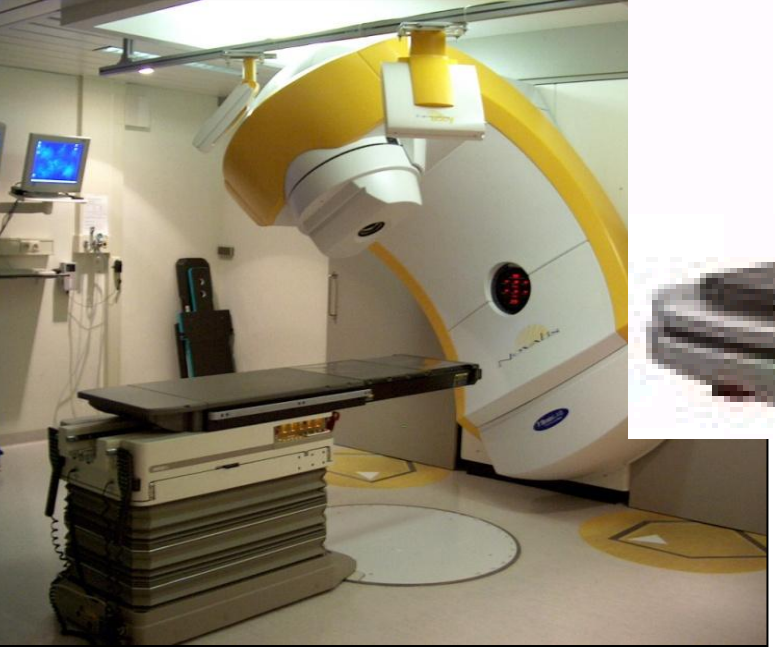
Definition
What's different ?



- "Reference frame"
- Precision < 1 mm (tracking)
- Multiple beams (non coplanar ?)
- Specific dose Distribution (+ MC)
- Limited target volume

= High dose/few fractions





SBRT=

we have

the tools !!!!

Academic radiotherapy department in 2013

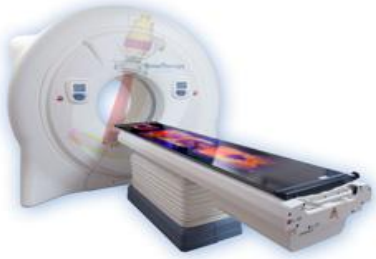
Centre Oscar Lambret

3D

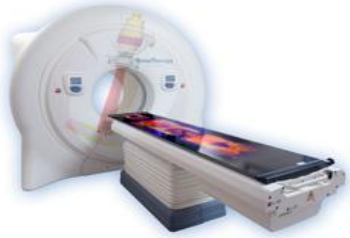
Varian Clinac 1

Varian Clinac 2

IG-IMRT



Tomo HDA 1



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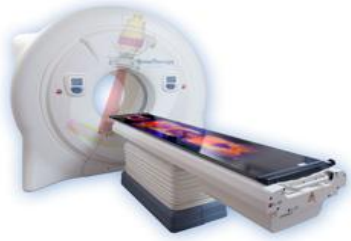


Tomo HDA 3

STEREO

CyberKnife

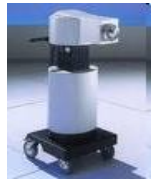
Gammaknife

Toshiba Aquilion

Nucletron Simulix

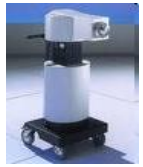
Nucletron Oncentra

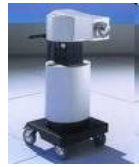
Aquilab



1 HDR

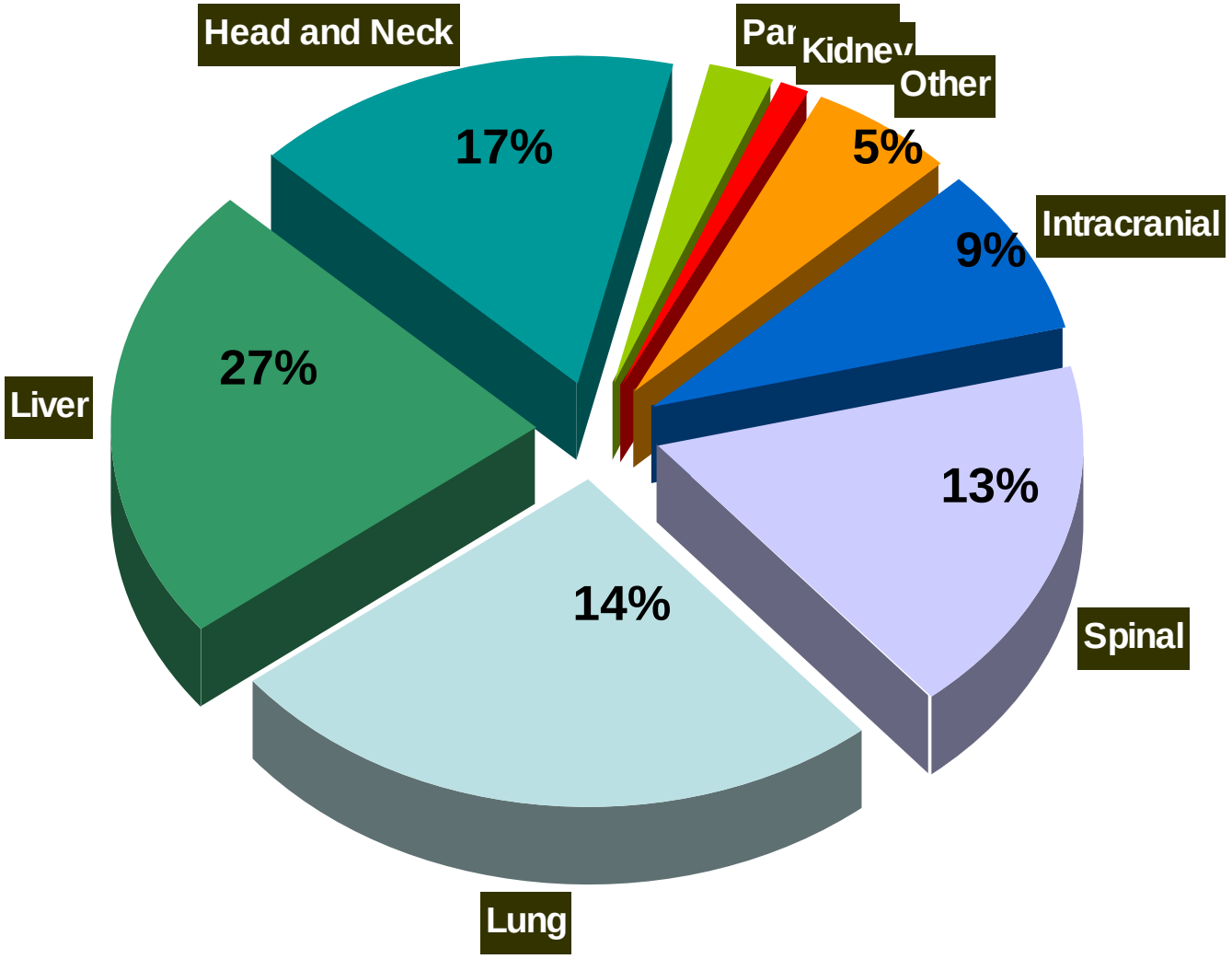
3 PDR





TYPE of LESIONS

1900 patients treated 06/207 to 12/2012



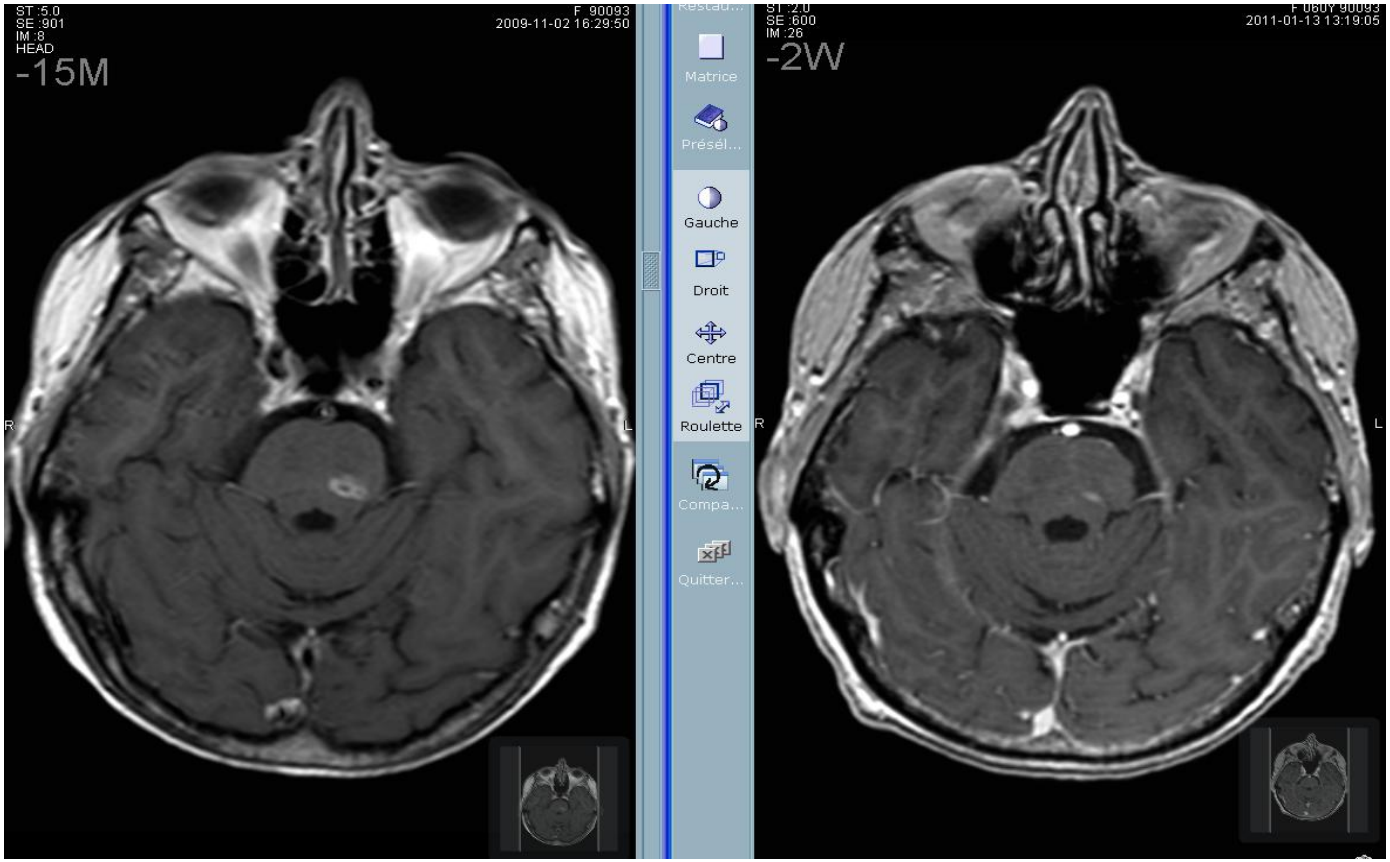
SBRT is a standard in many clinical situations

Centre Oscar Lambret

- **Today** : brain, lung, spine, retreatment
- **Tomorrow** : liver, prostate, partial breast …
- **After tomorrow** : most of ???

Brain metastases : role of radiosurgery/stereotactic RT

Initial treatment & re-irradiation



02/11/2009 **13/01/2011**

Breast cancer metastase

1982 : whole brain 10 X 3 Gy

Revue Neurologique
Volume 167, Issue 2, February 2011, Pages 185–186

SPINE

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Lettre à l'éditeur

Métastase intramédullaire unique d'un mésothéliome pleural traitée par radiothérapie stéréotaxique robotisée CyberKnife®

Solitary intramedullary metastasis from malignant pleural mesothelioma treated with CyberKnife®: A case report

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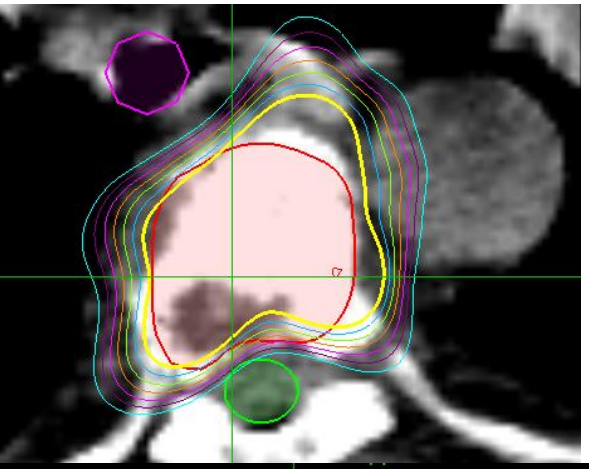
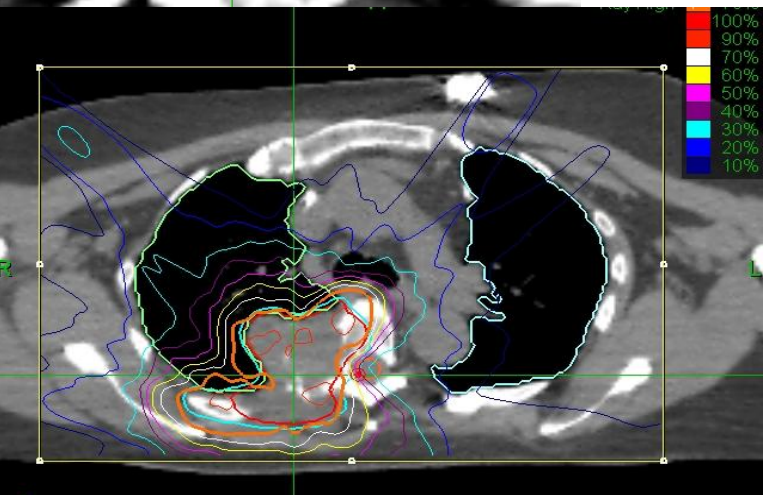
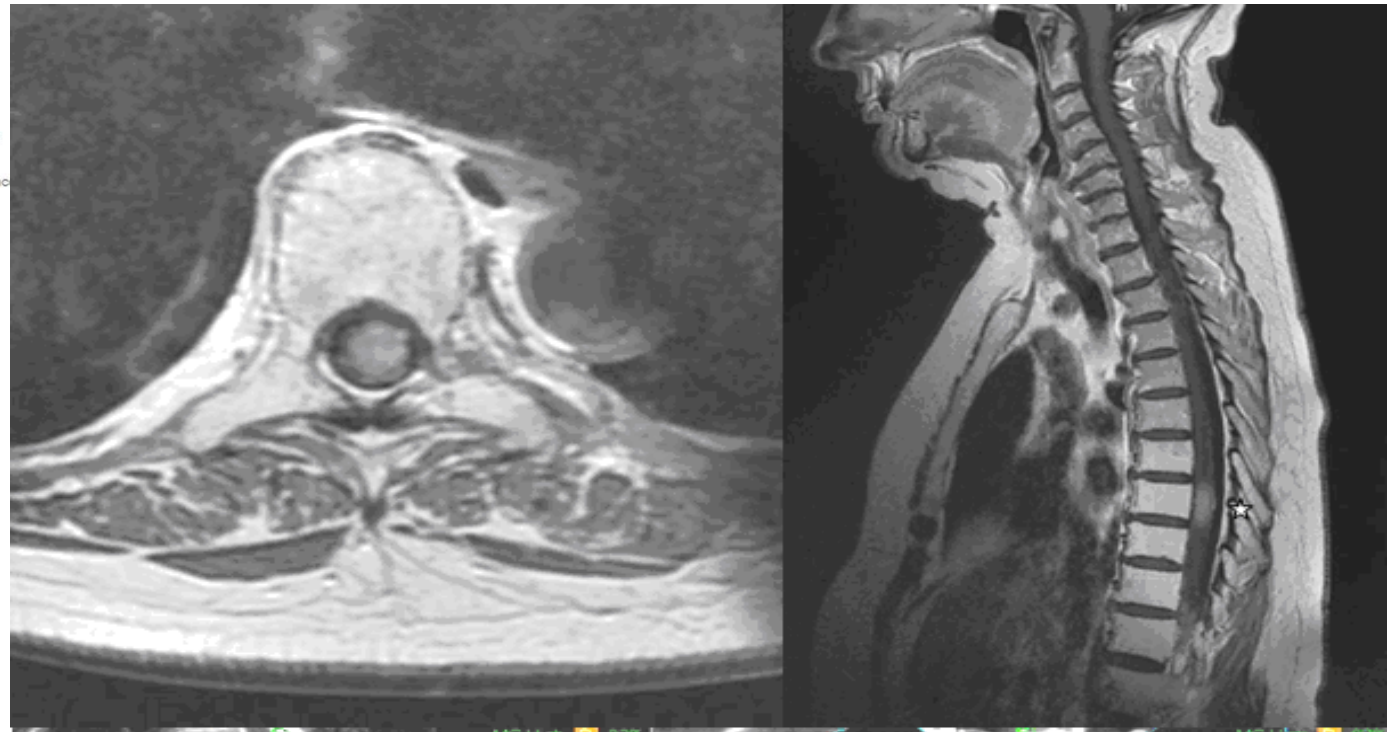
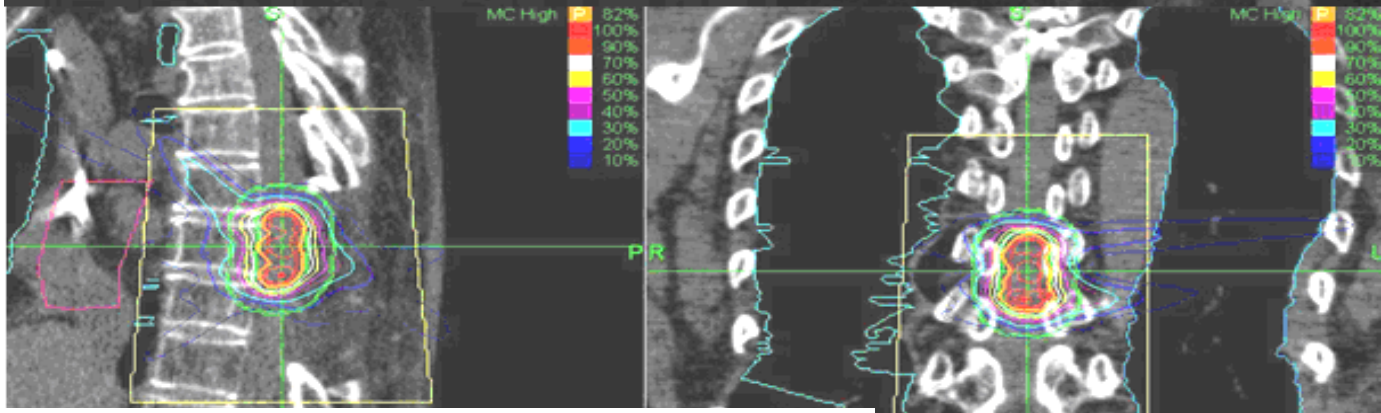
[c] Département de neurochirurgie, CHRU, université Lille II, 59000 Lille, France
[d] Département d'oncologie général, CLLC Oscar-Lambret, université Lille II, 59020 Lille, France





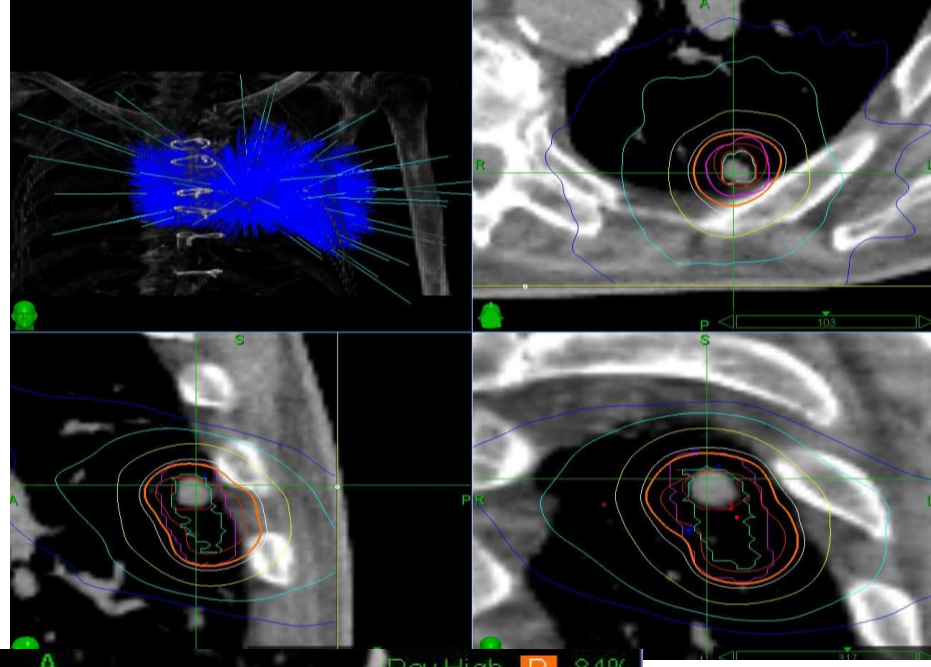


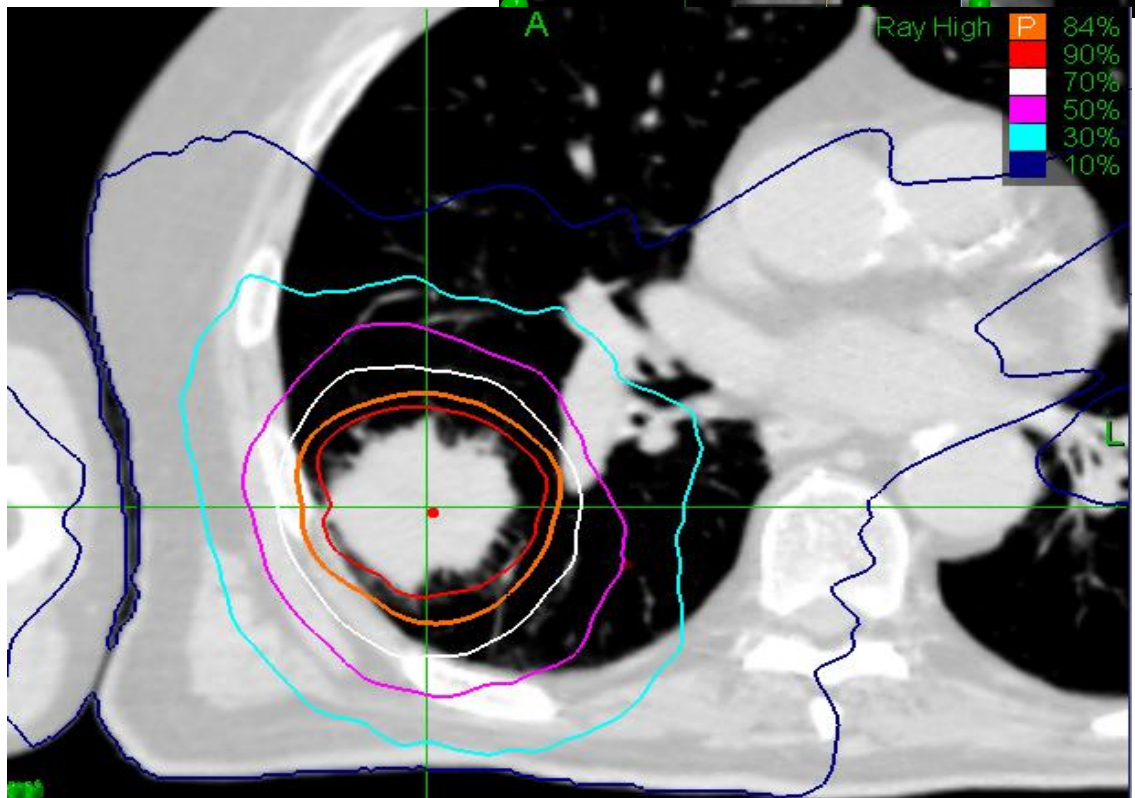


Spinal Mesothelioma metastase

Lung tracking

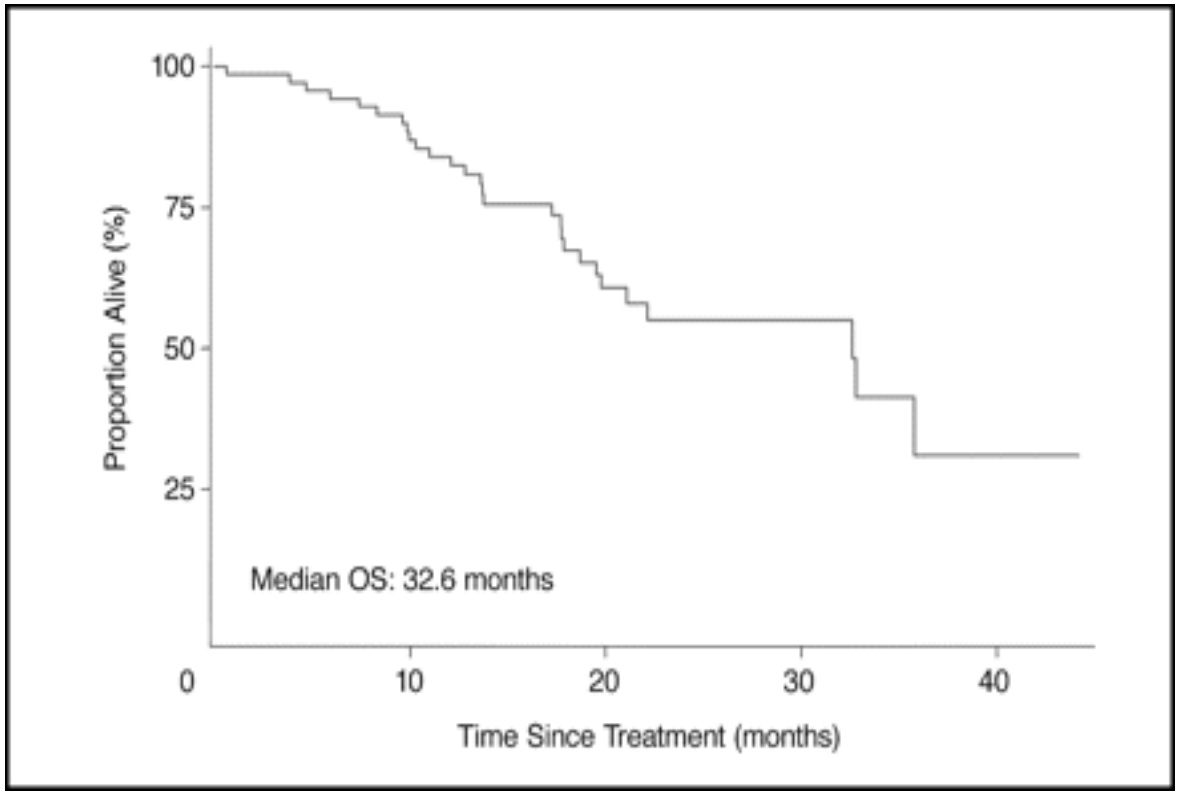
- Fiducial
- Fiducial less
  - Peripheral
  - > 15 mm
  - ITV





RTOG phase II evidence

- T1-2N0MO
- 70 pts NSCLC
- 60-66Gy
- 1-2 weeks
- 3 fractions
- LC 2y 95%
- OS 2y 55%
- 20% > G3 Toxicity
- 6† RT related toxicity



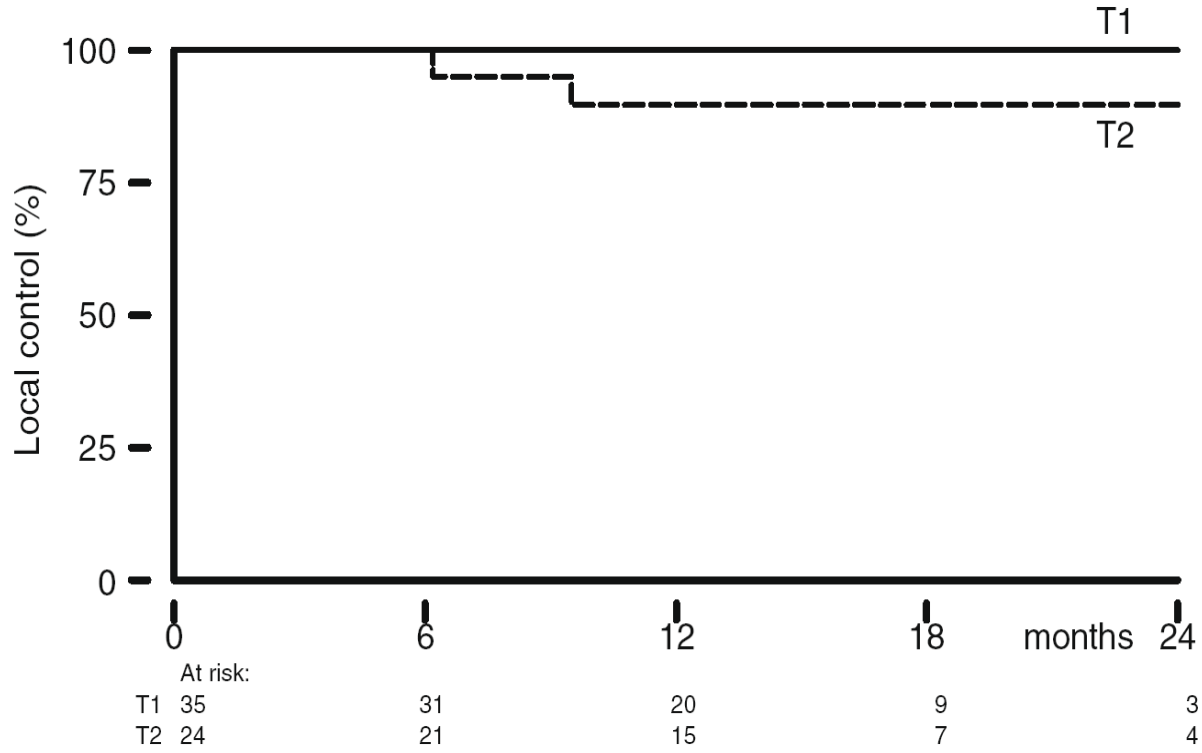
Timmerman et al, JCO 2006

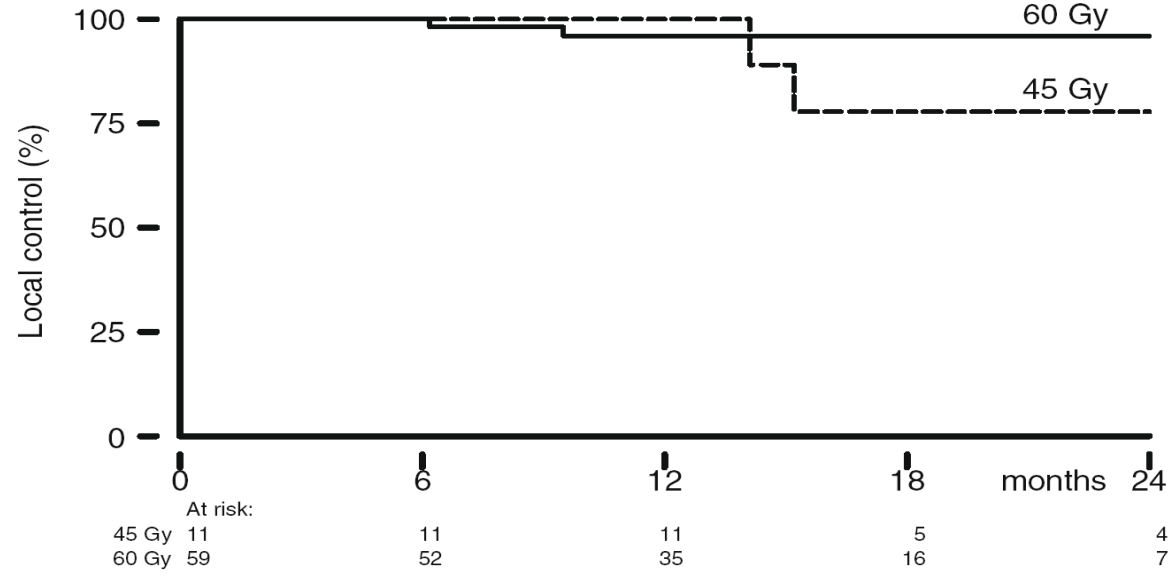
Rotterdam 59 patients fiducials

- 60 Gy
- T1 n = 35
- T2 n = 24
- p = 0.085

van der Voort van Zyp : Radiother Oncol 2009

ON GOING PHASE III STARS





	Number of patients	Stage	Design	Median follow-up (months)	Biopsy proven, n (%)	Dose fractionation	Medically operable, n (%)	Any toxicity ≥grade 3, n (%)	Local control	Survival
Kyoto University, Japan[28]	45	T1–2 N0M0	P	30	45 (100)	4×12 Gy	18 (40)	0	94% at 3 y	T1: 83% OS at 5 y; T2: 72% OS at 5 y
Stanford University, USA[29]	20*	T1–2 N0M0	P	18†	20 (100)	1×15–30 Gy	NA	4(12·5)‡	92% at 1 y§	85% OS at 1 y
Aarhus University, Denmark[30]	40	T1–2 N0M0	PM	28·8	39 (97·5)	3×15 Gy	0	NA	85% at 2 y	48% at 2 y
Indiana University, USA[21]	70	T1–2 N0M0	P	17·5	70 (100)	3×20–22 Gy	0	14 (20)	95% at 2 y	54·7% OS at 2 y
RTOG 0236, USA[22]	55	T1–3 N0M0	PM	8·7	55 (100)	3×20 Gy	0	10 (18)	NA	NA
University of Heidelberg, Germany[31]	42‖	T1–3 N0M0	PR	15	42 (100)	1×19–30 Gy	0	0	68% at 3 y	37% OS at 3 y
Tohoku University, Japan[32]	31	T1–2 N0M0	P	32	31 (100)	3×15 Gy or 8×7·5 Gy	11 (35)	1 (3·2)	T1: 78% at 3 y; T2: 40% at 3 y	72% OS at 3 y
Karolinska University, Sweden[33]	57	T1–2 N0M0	PM	23	38 (67)	3×15 Gy	0	12 (21)	96% crude rate	65% crude rate
VU University, Netherlands[27]	206	T1–2 N0M0	PD	12	64 (31)	3–8× 7·5–20 Gy	39 (19)	6 (3)	93% at 2 y	64% OS at 2 y

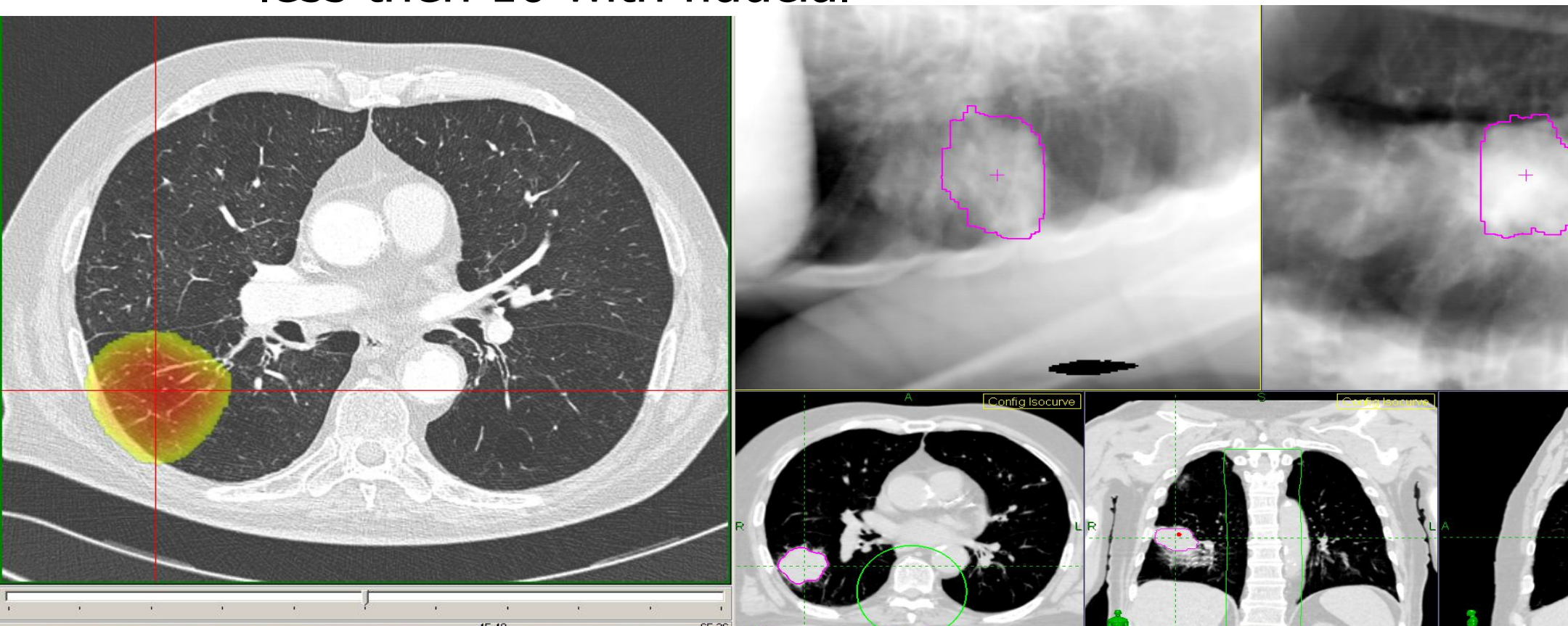
P=prospective trial. PR=prospective and retrospective reported together. PM=prospective multicentre. PD=prospecty Group. T1=American Joint Committee on Cancer tumour stage 1. T2=American Joint Committee on Cancer tumour stage 2. NA=not availhrolled patients with lung metastases. †For living patients. ‡Data not limited to early stage NSCLC patients. §For patients receiving greater thaphase 1–2 protocol.

Table 1: **Prospective studies of SBRT for early stage NSCLC**

Fiducial less

Between may 2008 and now :

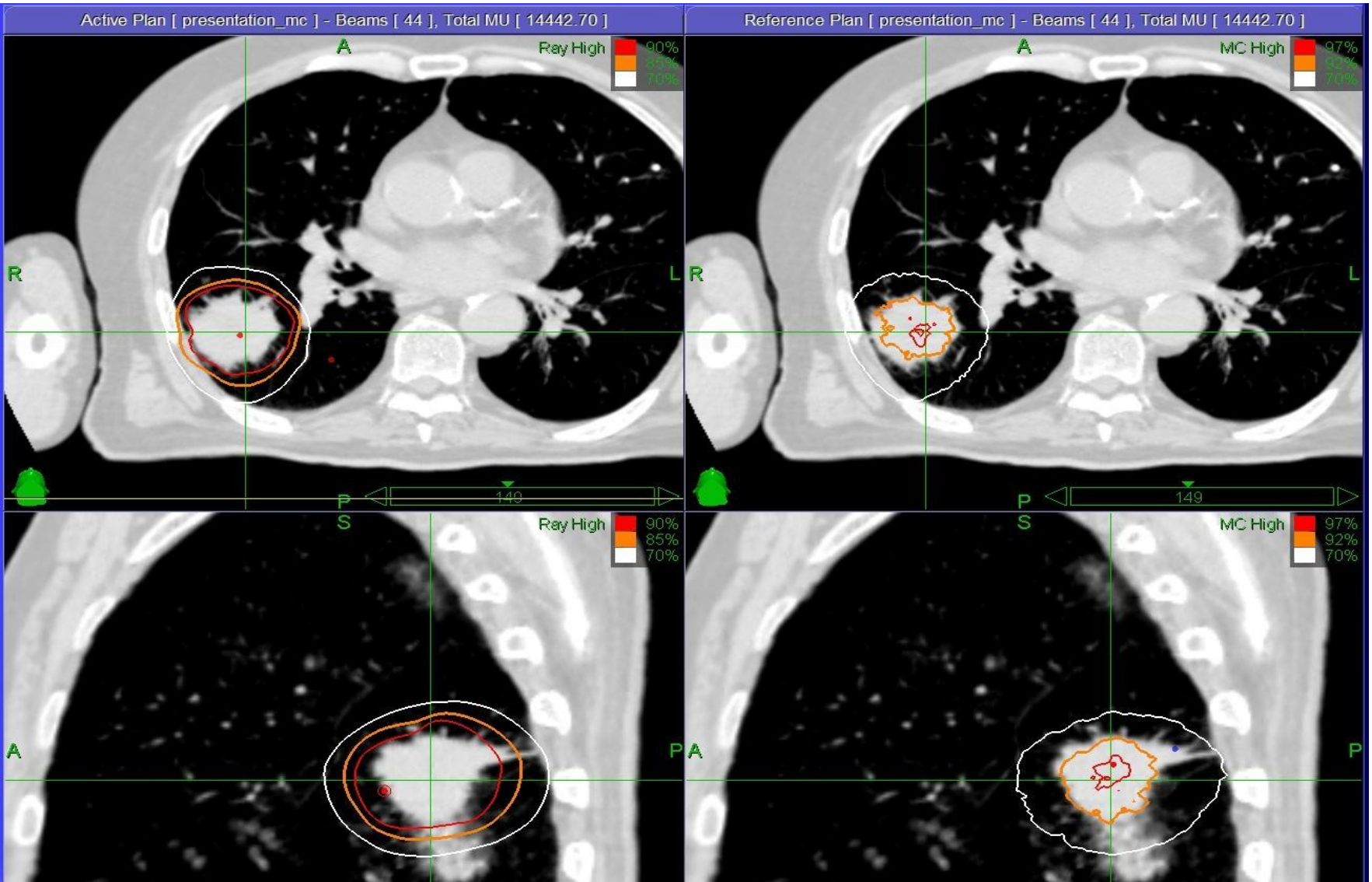
- about 50 patients with xsight_lung
- about 60 patients with xsight_spine
- less then 10 with fiducial



Lung

Ray-Tracing : 3 x 20 Gy

Monte-Carlo :



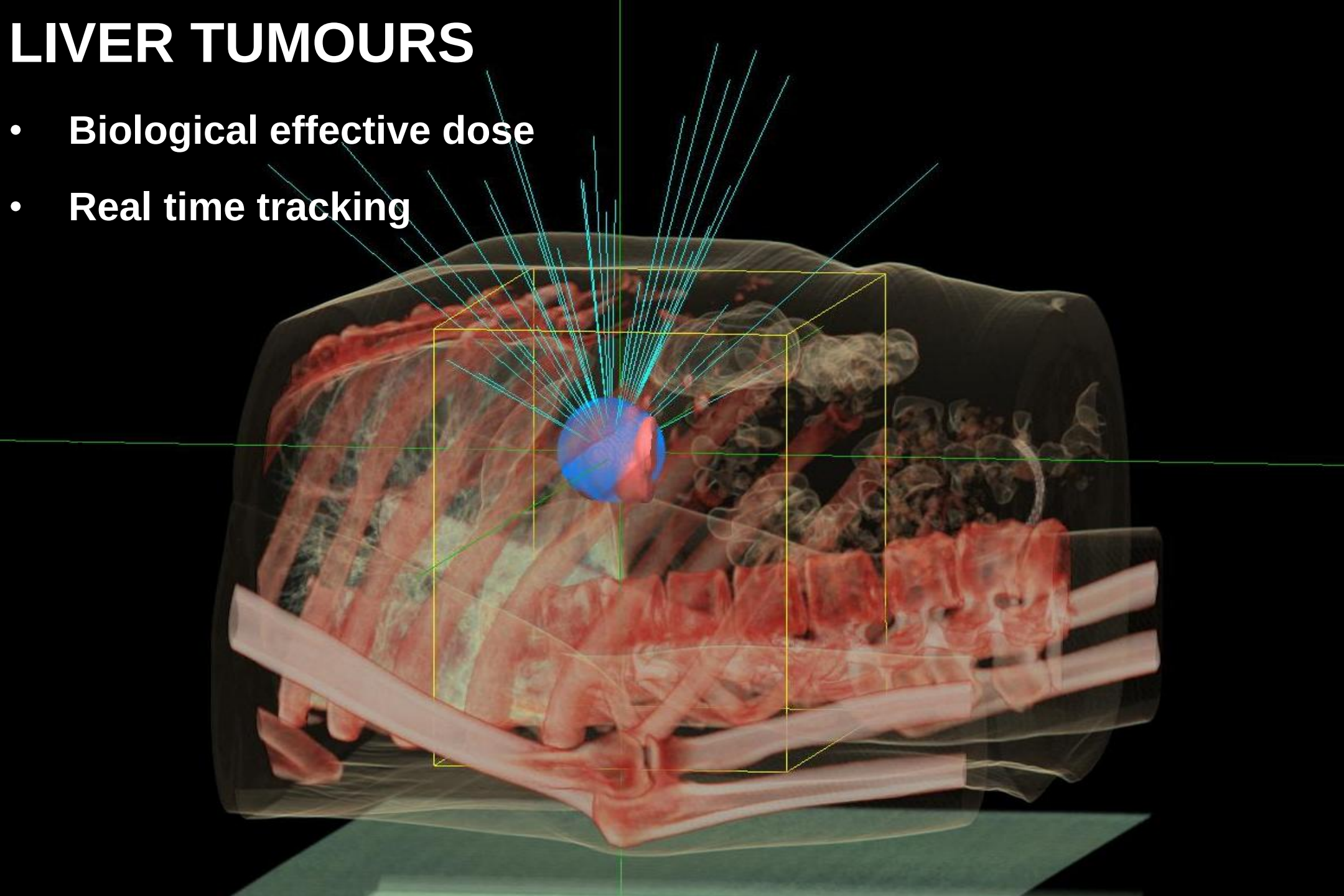
— 63.5 Gy

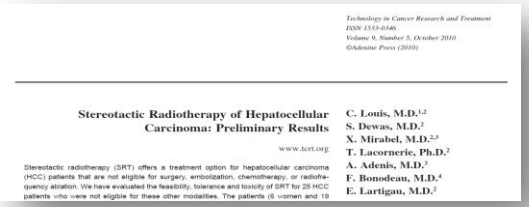
— 60.0 Gy

— 50.0 Gy

LIVER TUMOURS

- Biological effective dose
- Real time tracking





Technology in Cancer Research and Treatment
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Volume 9, Number 5, October 2010
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Stereotactic Radiotherapy of Hepatocellular Carcinoma: Preliminary Results

C. Louis, M.D.[1,2]
S. Dewas, M.D.[1]
X. Mirabel, M.D.[2,3]
T. Lacornerie, Ph.D.[2]
A. Adenis, M.D.[3]
F. Bonodeau, M.D.[4]
E. Lartigau, M.D.[2]

www.tcrt.org

Stereotactic radiotherapy (SRT) offers a treatment option for hepatocellular carcinoma (HCC) patients that are not eligible for surgery, embolization, chemotherapy, or radiofrequency ablation. We have evaluated the feasibility, tolerance and toxicity of SRT for 26 HCC patients who were not eligible for these other modalities. The patients (6 women and 19

120 patients / 153 Liver tumours

Centre Oscar Lambret

HCC 48

Mets 99

Cholangio… 6

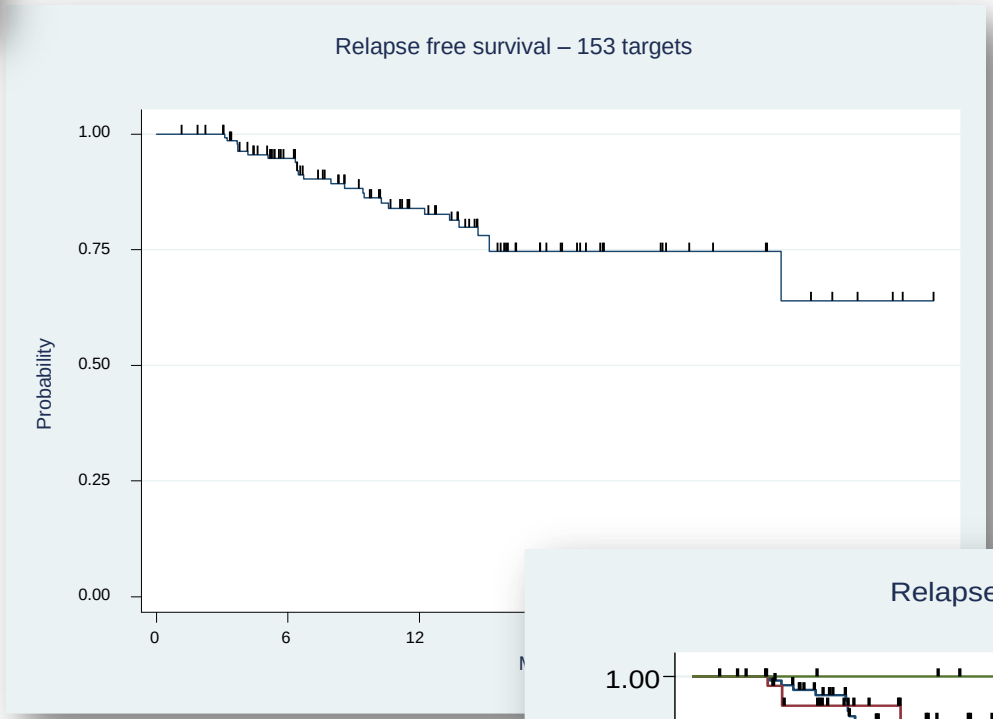
LC

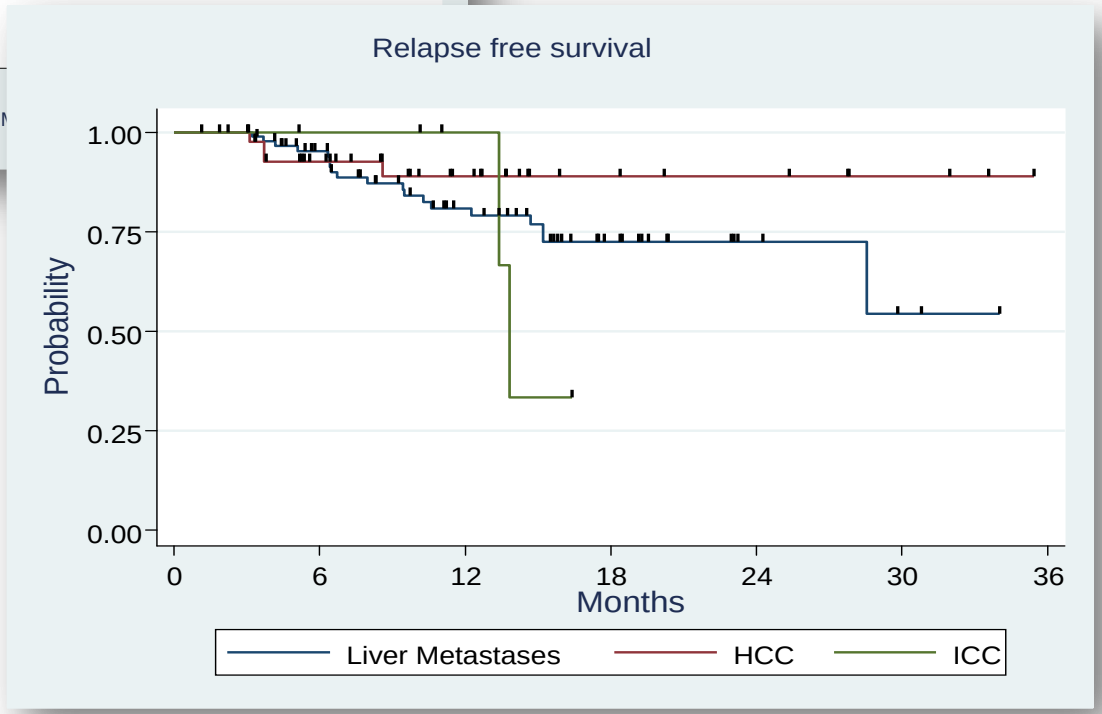
1 year 84 %

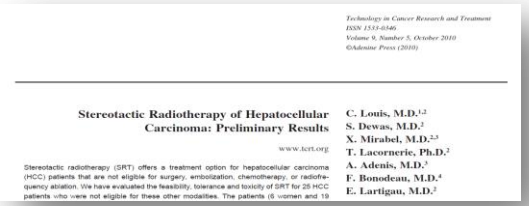
(CI 95% : 75.6 – 89.7%)

2 years 75 %

(CI 95% : 63.7 – 82.7%)







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Toxicity Grade 3-4

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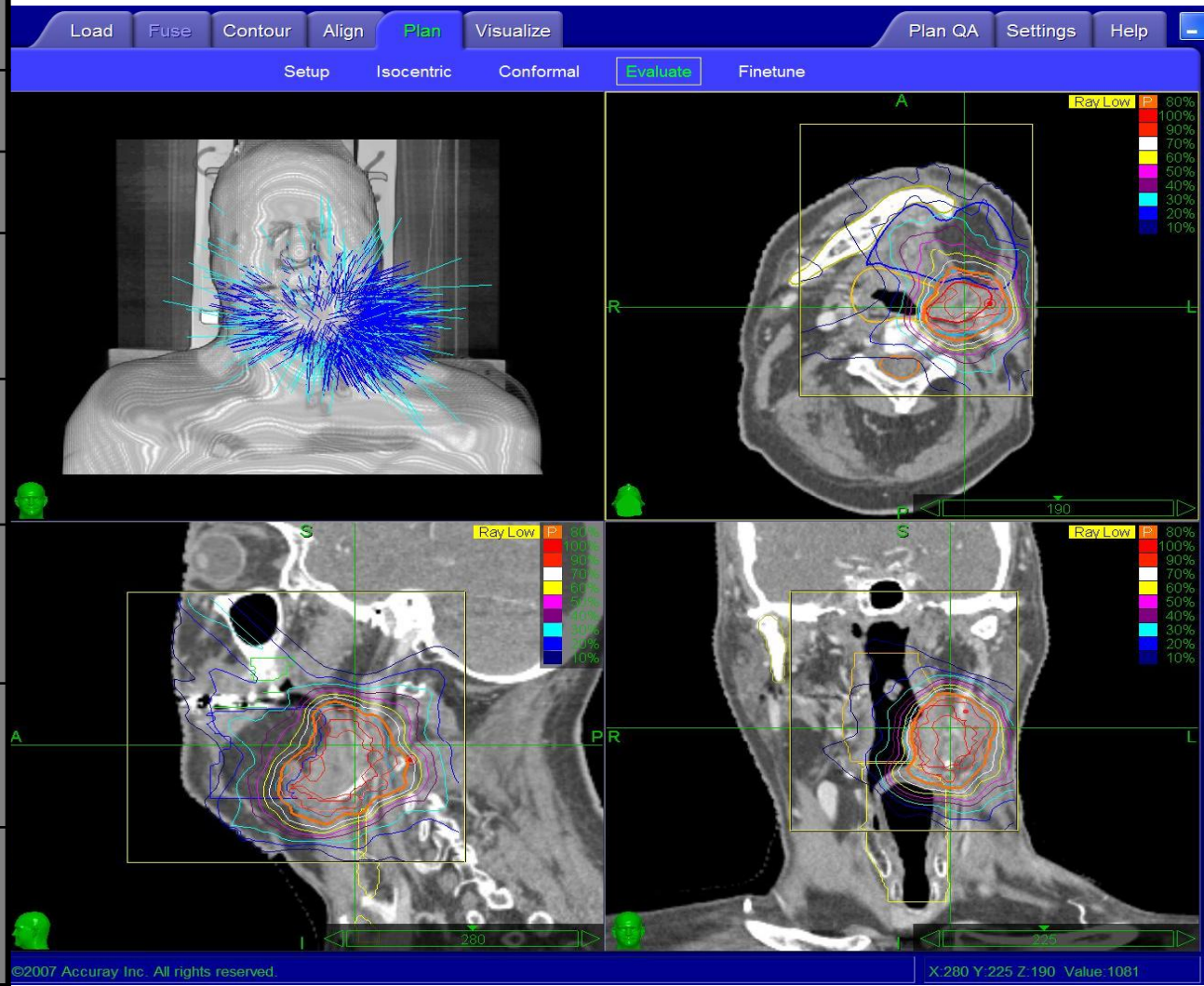
- 120 patients HCC + metastases

• Duodenal ulcer	6	5 %
• Othesr	6	5 %
– skin		
– Liver pain		
– Asthenia		
• RILD	2 ?	

RETREATMENT

- 6 Gy X 6 in 12 days
- Isodose 80% : 95% of PTV
- Cetuximab (400 +250 mg/m^2 x 4)

X Sight Spine	35
Skull 6D	10
Fiducials	1
Volume GTV cm^3	Median **29**
Volume PTV cm^3	Median **60**
Beams	Median **156** (103-225)
Collimators	1
Duration	Median **48 min** (28-100)



Multicentric phase II

Lille, Nancy, Nice

Best response, n (%)	N=49
Complete Response	24 (49.0)
Partial Response	10 (20.4)
Stable Disease	11 (22.5)
Progressive Disease	4 (8.2)

Median overall response duration was 7.9 months

Overall objective best response rate : 69.4% [95% CI: 54.6-81.7%]

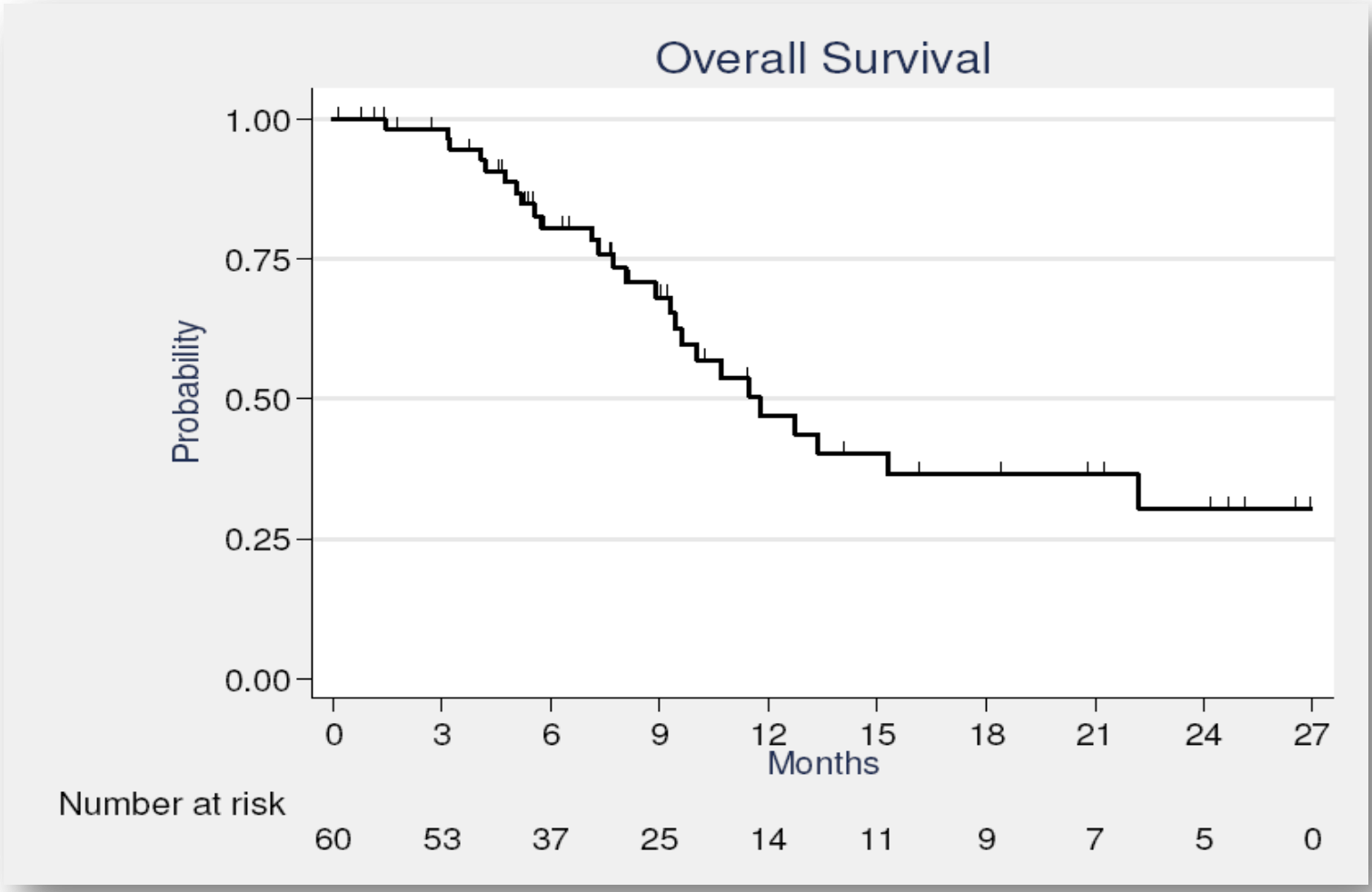
Disease control rate : 91.8% [95% CI: 80.4-97.7%]

Safety Results

- **Deaths**
  - One death from hemmorage and denutrition not related to study drug
- **Serious adverse events**

Relationship		AE	Grade	Consequence	Delay start SAE (months)	Patient ID
Certain	RT+CT	Aphagia	3	Hospitalization	3.7	310
Probable	RT+CT	Deshydratation	3	Hospitalization	1.9	116
Probable	RT+CT	Respiratory distress	4	Hospitalization	1.8	202
Possible	RT	Oropharynx edema	-	No	7.3	202
Doubtful	RT+CT	Pulmonary infection	4	Hospitalization + treatment interruption	0.3	207
No		Hemorrhage	2	Hospitalization	0.1	106
No		Weight loss	3	Hospitalization	0.2	106
No		Stomach perforation	3	Hospitalization	1.9	107
No		Gastro intestinal	1	Hospitalization	0.7	130
No		Septicemia	-	Hospitalization + treatment interruption	0.7	203

Overal survival



The one-year OS rate is 47.5% (95%CI: 30.8-62.4).

The median survival is 11.8 months (95%CI: 9.3 - 22.2)

Dewas et al. Radiation Oncology 2011, 6:77
http://www.ro-journal.com/content/6/1/77

RADIATION ONCOLOGY

RESEARCH Open Access

Robotic image-guided reirradiation of lateral pelvic recurrences: preliminary results

Sylvain Dewas[1], Jean Emmanuel Bibault[1], Xavier Mirabel[1,2], Philippe Nickers[1,3], Bernard Castelain[1,3], Thomas Lacornerie[1], Hajer Jarraya[4] and Eric Lartigau[1*]

Table 1 Characteristics of patients treated with CyberKnife for pelvic re-irradiation.

	Number (%)	Mean (range)	Comments
Patients	16		
Sex (M/F)	6 (37%)/10 (63%)		
Age*	55	(34 - 70 y.o.)	
Primary disease			
Anal canal	6 (38%)		
Cervix	4 (25%)		
Uterus	1 (6%)		
Rectum	4 (25%)		
Bladder	1 (6%)		
Primary treatment			
Surgery	9 (56%)		
Chemotherapy	13 (81%)		9 concomitant; 4 adjuvant
Radiotherapy	14 (87%)		
Dose*		45 Gy (20-75 Gy)	
Eq D2*			
Early side effects (α/β = 3 Gy)		45 Gy (33-58 Gy)	
Late side effects (α/β = 10 Gy)		72 Gy (53-96 Gy)	
Treatment of the recurrence			
Surgery	6 (38%)		
Chemotherapy	8 (50%)		
Radiotherapy	3 (19%)		
Dose*		53.7 Gy (36-66 Gy)	
Eq D2*			
Early side effects (α/β = 3 Gy)		65 Gy (45-66 Gy)	
Late side effects (α/β = 10 Gy)		106 Gy (72-110 Gy)	

* Median value

Dewas et al. Radiation Oncology 2011, 6:77
http://www.ro-journal.com/content/6/1/77

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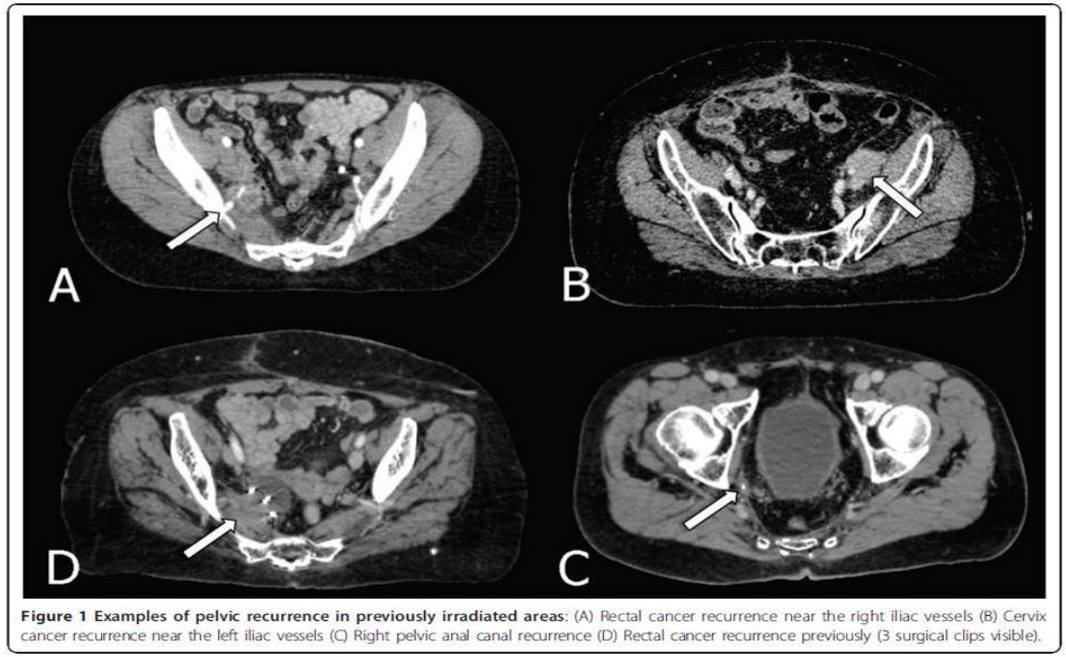

Figure 1 Examples of pelvic recurrence in previously irradiated areas: (A) Rectal cancer recurrence near the right iliac vessels (B) Cervix cancer recurrence near the left iliac vessels (C) Right pelvic anal canal recurrence (D) Rectal cancer recurrence previously (3 surgical clips visible).

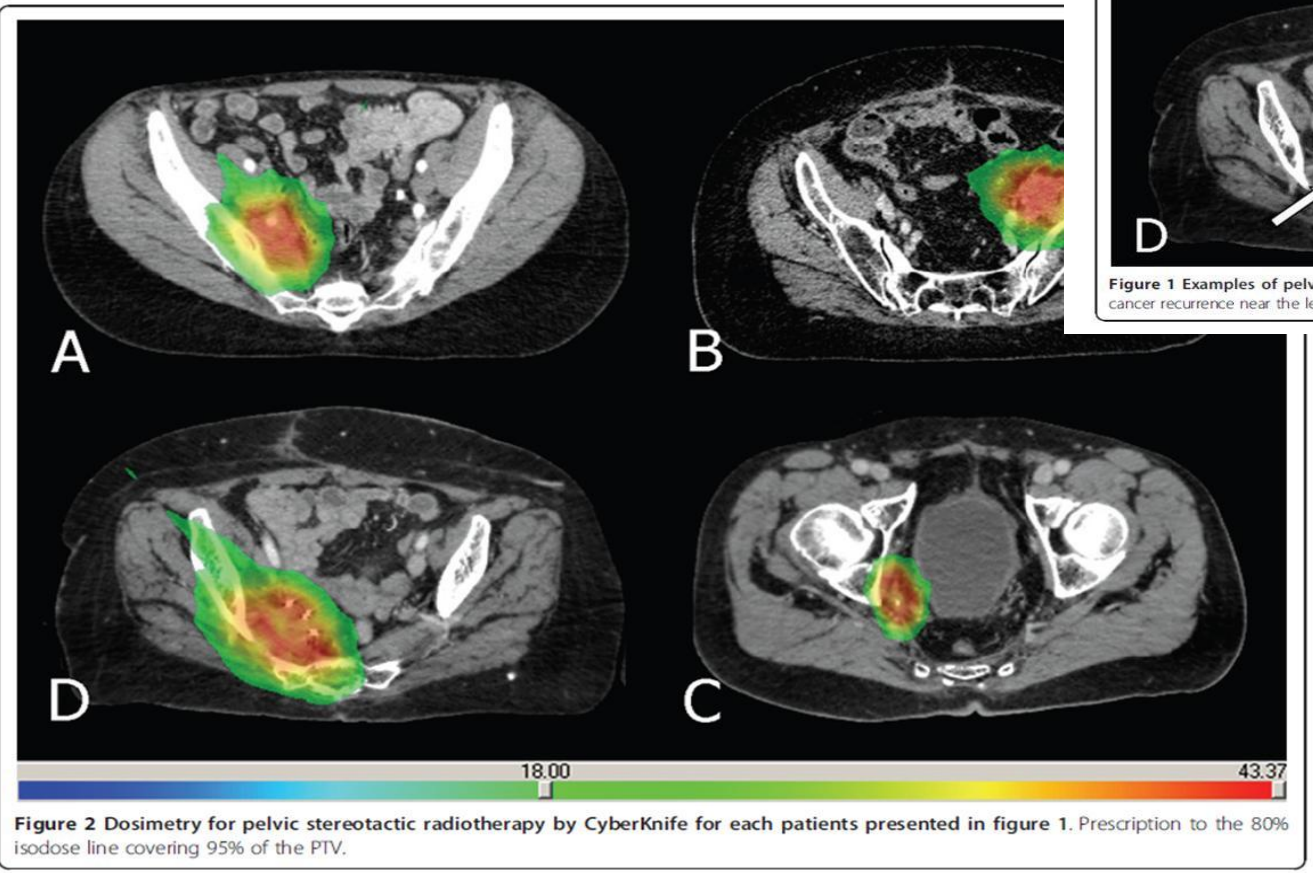

Figure 2 Dosimetry for pelvic stereotactic radiotherapy by CyberKnife for each patients presented in figure 1. Prescription to the 80% isodose line covering 95% of the PTV.

- **Median F Up 10,6 months**
- **LC & year 70%**

OLIGOMETASTASES

Centre Oscar Lambret

Local treatment : an issue ?

Concept of ablative treatments

- **Surgery : (brain, liver) brings long survival….**
  - **Radiosurgery/SBRT (brain), liver, lung, nodes…….**

Rational

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- Cure is T N dependent
- When M : no cure ! (solid tumours in adults)

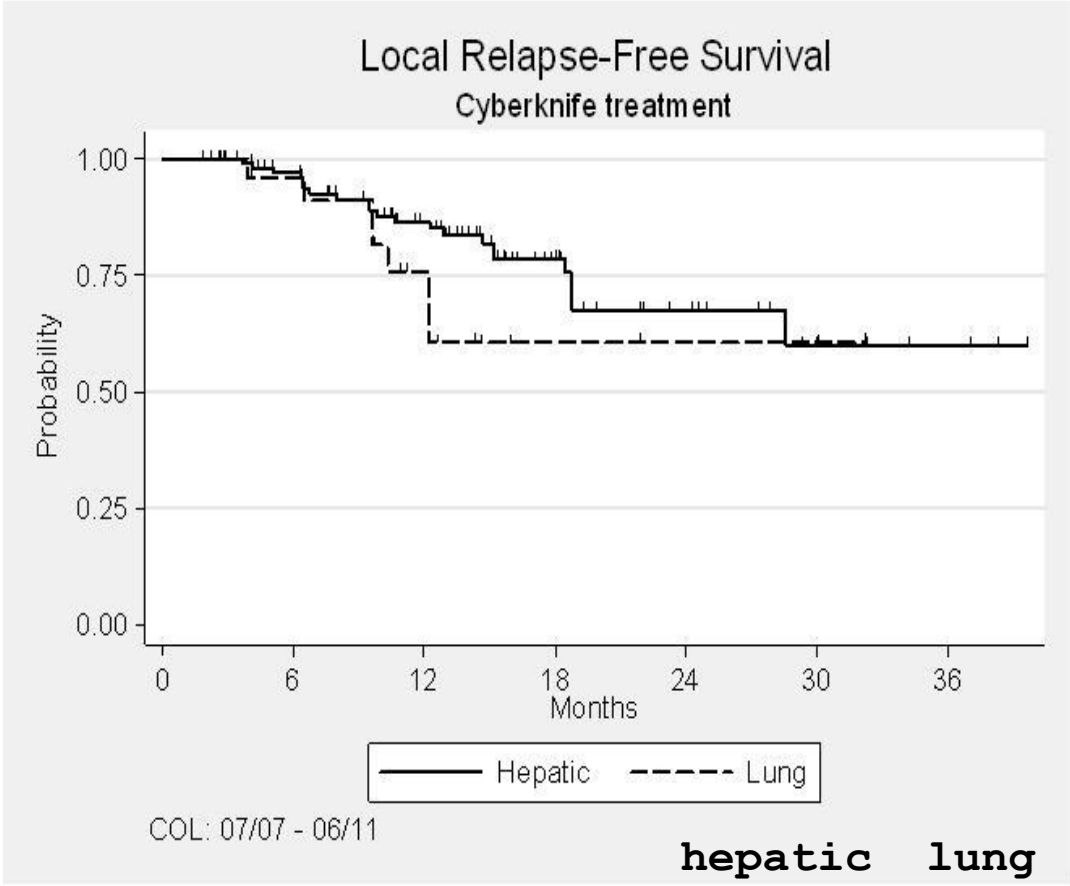
- Successive treatment(ssss) (targeted) may bring long term local control of M (liver, lung, brain…)

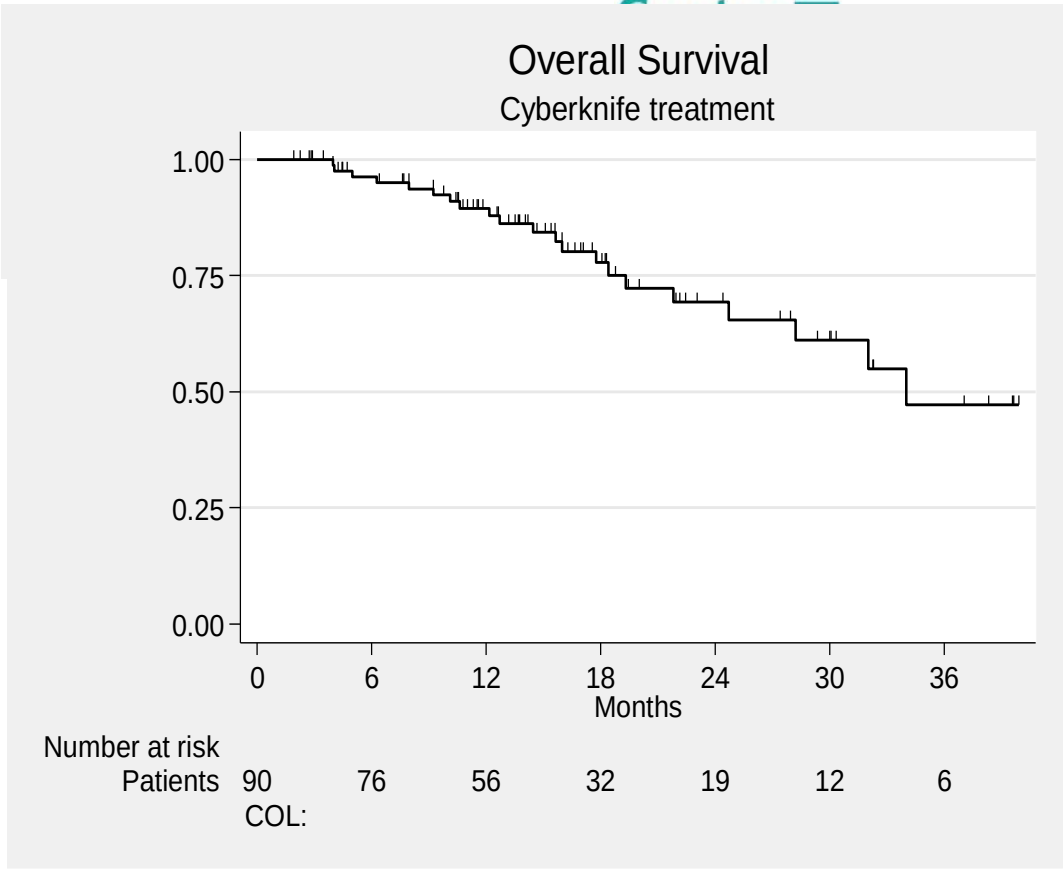
Role of combined/sequential systemic and loco-regional treatment (surgery/radiotherapy) ???

When, how ?

SBRT : liver/lung metastases

- SBRT experience in Lille
- 06/2007 to 06/2010 : **90** patients on **850**
- Median age : 65
- 139 lesions
- 2/3 gastro intestinal primary





	hepatic	lung
12 months	0.8649	0.7577
24 months	0.6758	0.6062

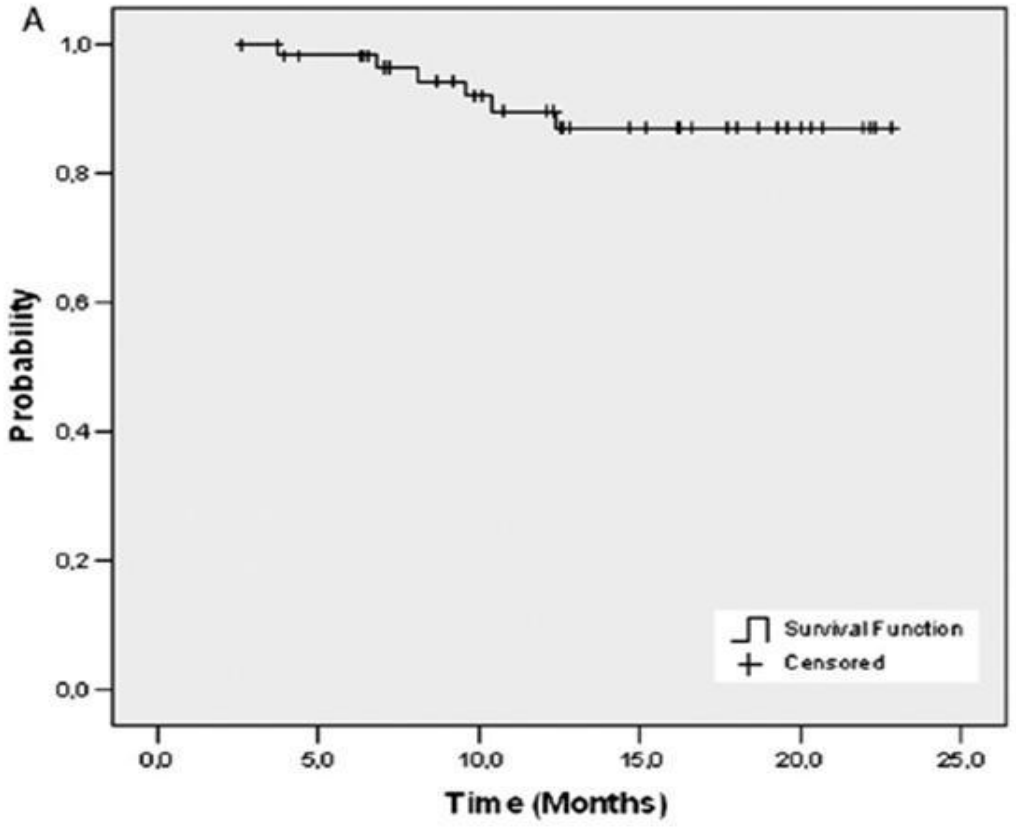
Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 3, pp. e39–e47, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.12.047

IMAGE-GUIDED ROBOTIC STEREOTACTIC BODY RADIATION THERAPY FOR LIVER METASTASES: IS THERE A DOSE RESPONSE RELATIONSHIP?

Claire Vautravers-Dewas, M.D.,*† Sylvain Dewas, M.D.,* François Bonodeau, M.D.,‡ Antoine Adenis, M.D., Ph.D.,¶ Thomas Lacornerie, Ph.D.,* Nicolas Penel, M.D.,¶ Eric Lartigau, M.D., Ph.D.,* and Xavier Mirabel, M.D.*



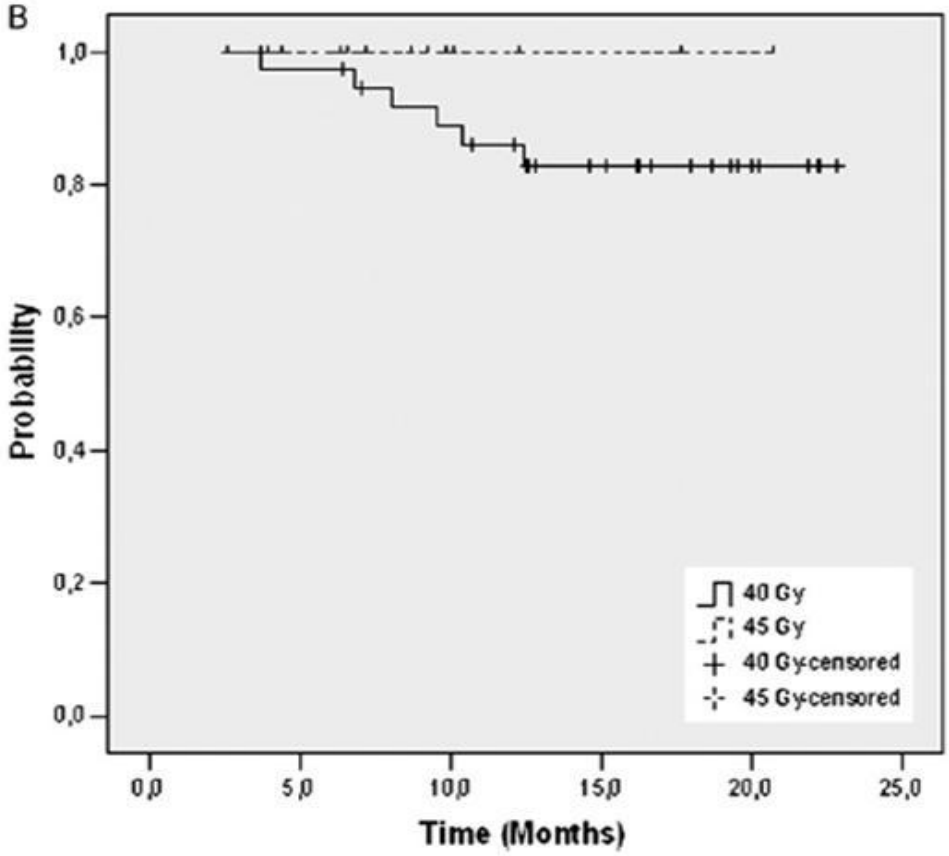


Fig. 1. Local control. (A) Local control. (B) Local control by dose.

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Lung Metastases

J Clin Oncol 27:1579-1584. © 2009

Kyle E. Rusthoven, Brian D. Kavanagh, Stuart H. Burri, Changhu Chen, Higinia Cardenes, Mark A. Chidel, Thomas J. Pugh, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter

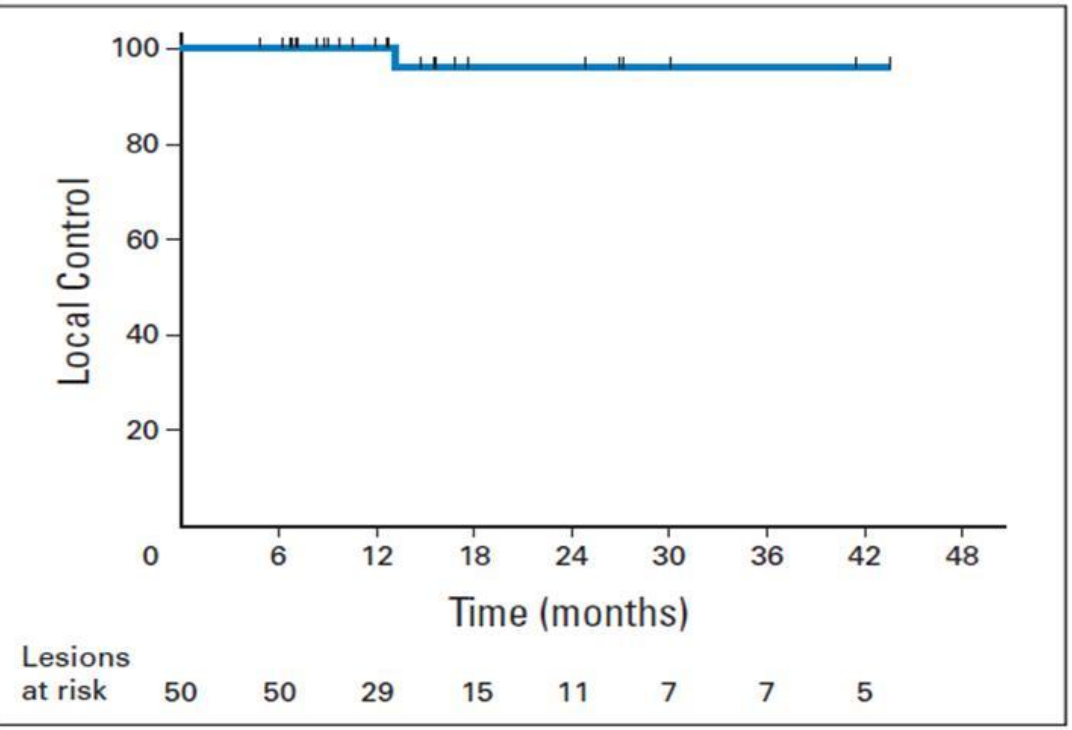


Fig 2. Actuarial local control in an assessable patient.

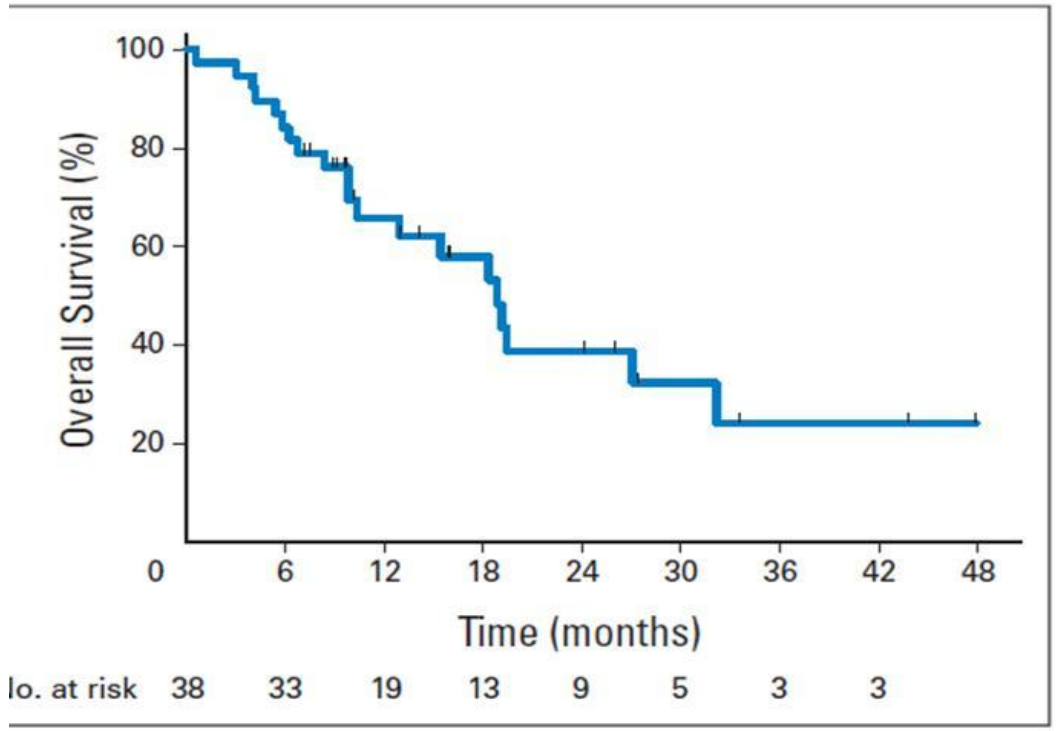


Fig 3. Actuarial survival for all patients.

Table 2. Details for Patients With Grade 3 Toxicity

Primary	Dose (Gy)	Grade 3 Toxicity	Clinical Details	SBRT Details
NSCLC	60	Pneumonitis	Increased dyspnea and oxygen requirement beginning 7 months after SBRT; CT changes consistent with pneumonitis; decrease in FeV_1 from 1,320 mL before SBRT to 740 mL after SBRT	Lung V15 was 15.4%
Sarcoma	60	Chest wall	Left 6th rib fracture on CT appearing 25 months after SBRT; patient had chest discomfort localized to the treated area, but did not require narcotic pain medication	Left 6th rib included in PTV; max dose to rib was 76.4 Gy at the site of fracture
SCC of base of tongue	60	Skin	Confluent moist desquamation appearing 6 weeks after SBRT; moderate pain, managed with NSAIDS; improved at 4 months follow-up	30 Gy isodose extended to within 1 mm of the skin surface, corresponding to area of skin desquamation

Abbreviations: SBRT, stereotactic body radiation therapy; NSCLC, non–small-cell lung cancer; CT, computed tomography; FeV_1, forced expiratory volume in 1 second; LV15, volume receiving 15 Gy and higher; PTV, planning target volume; SCC, squamous cell carcinoma; NSAIDS, nonsteroidal anti-inflammatory drugs.

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter

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LIVER

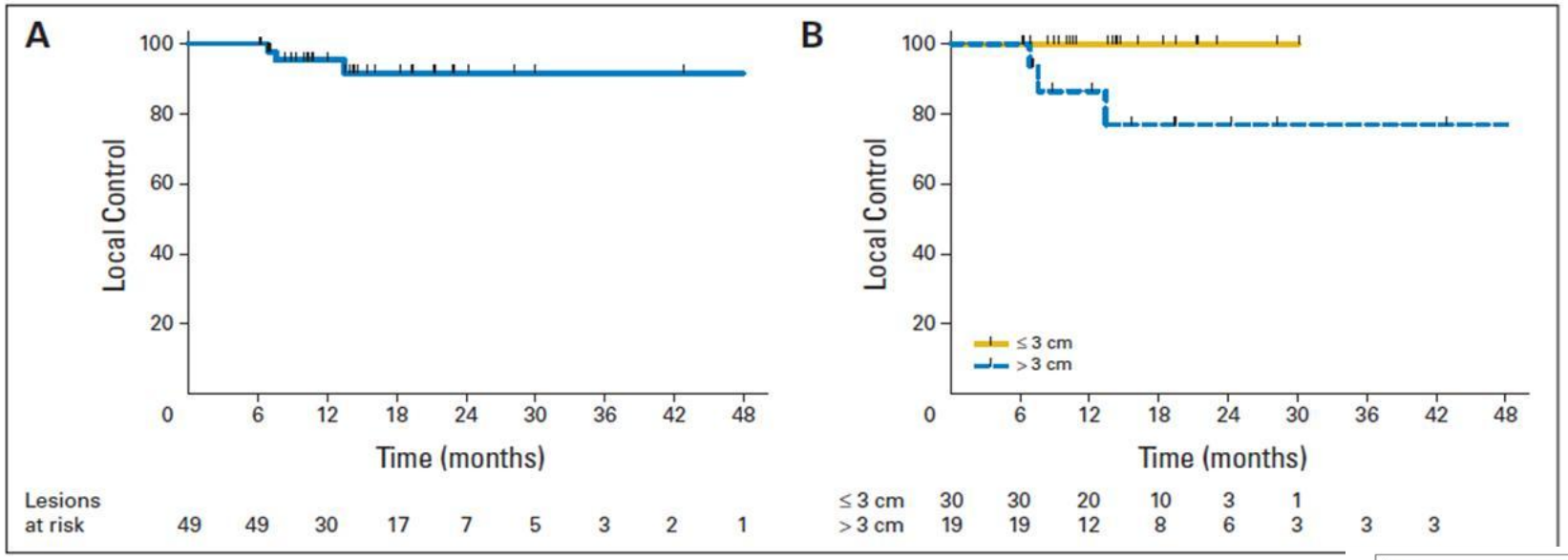


Fig 2. Actuarial local control for (A) all lesions and (B) lesions according to maximal tumor diameter.

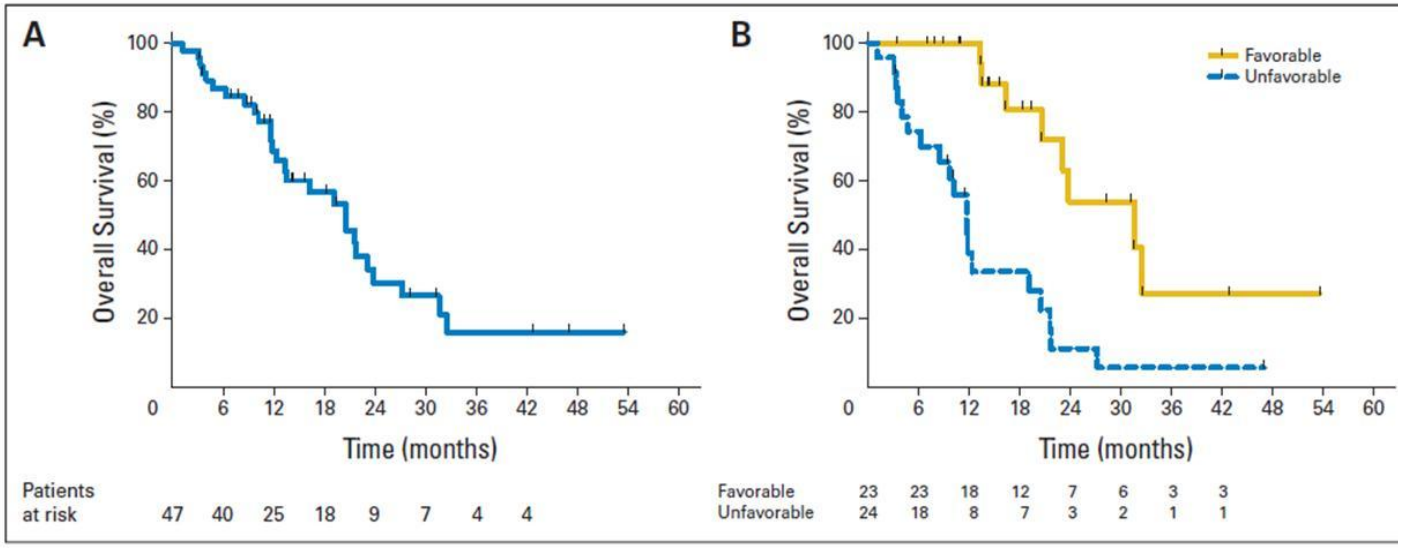
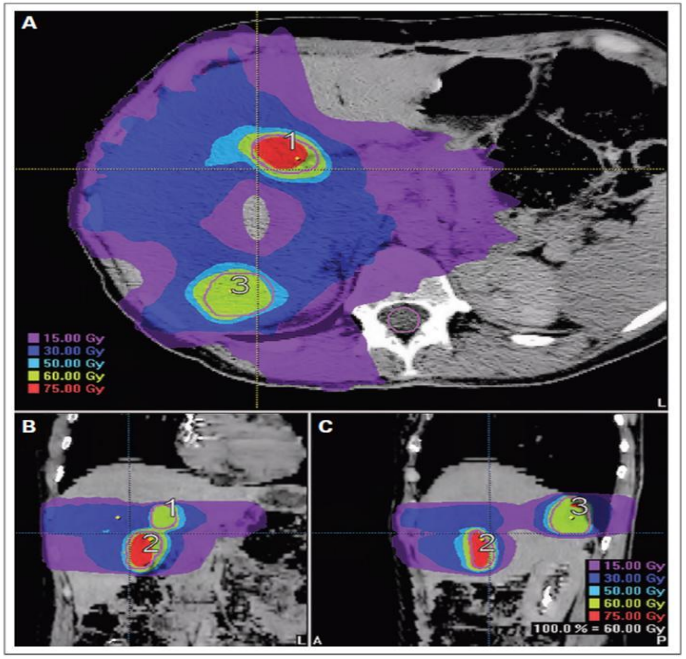


Fig 3. Actuarial survival for (A) all patients and (B) patients according to primary site.



PROSTATE

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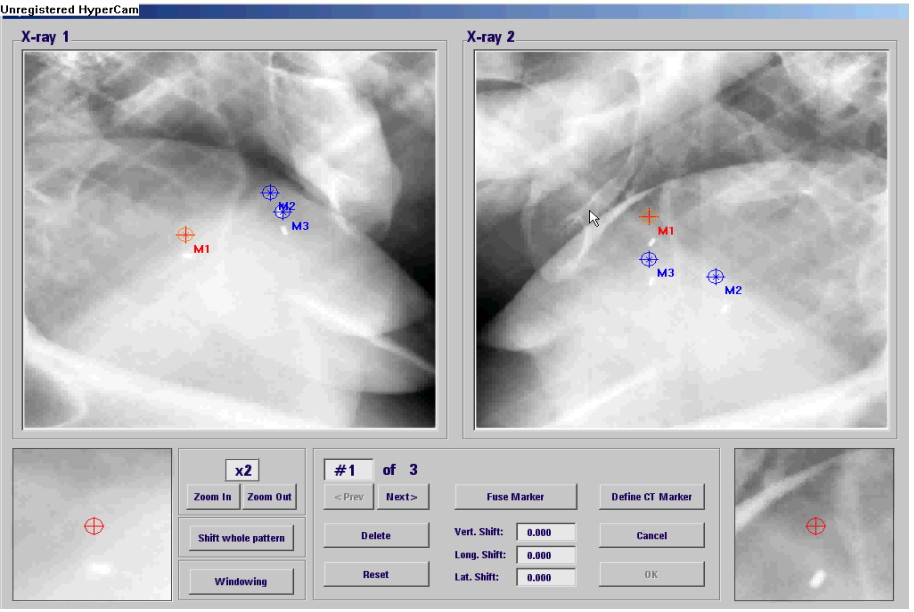
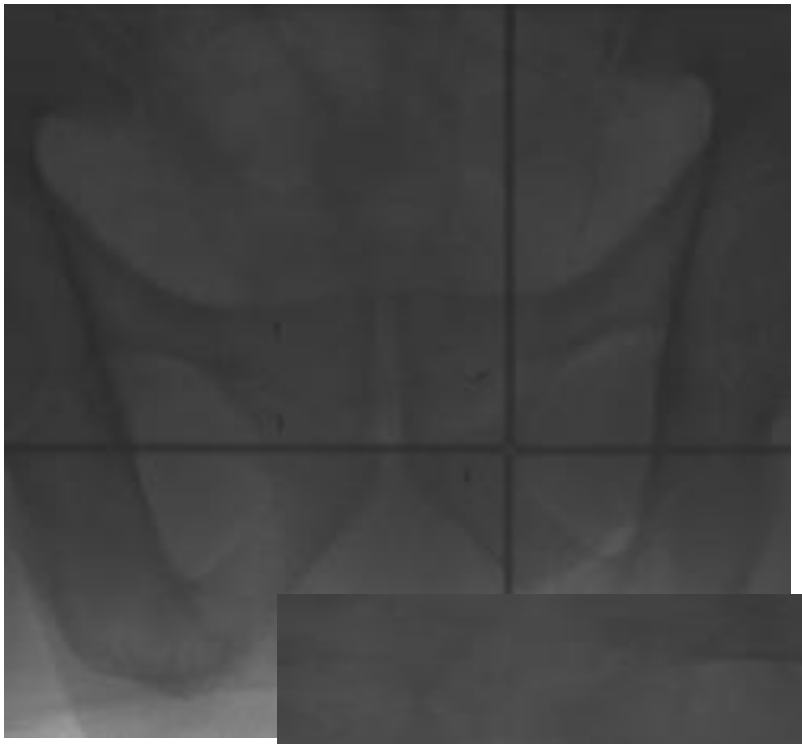




Stranded Fiducials

Patient Selection for Robotic Radiosurgery for Clinically Localized Prostate Cancer: Come One, Come All

Sean P. Collins, Simeng Suy, Eric Oermann, Siyan Lie, Xia Yu, Heather Hanscom, Joy Kim, Benjamin Sherer, Hyeon U. Park, Brian T. Collins, Kevin McGeagh, Nancy Dawson, John H. Lynch, and Anatoly Dritschilo

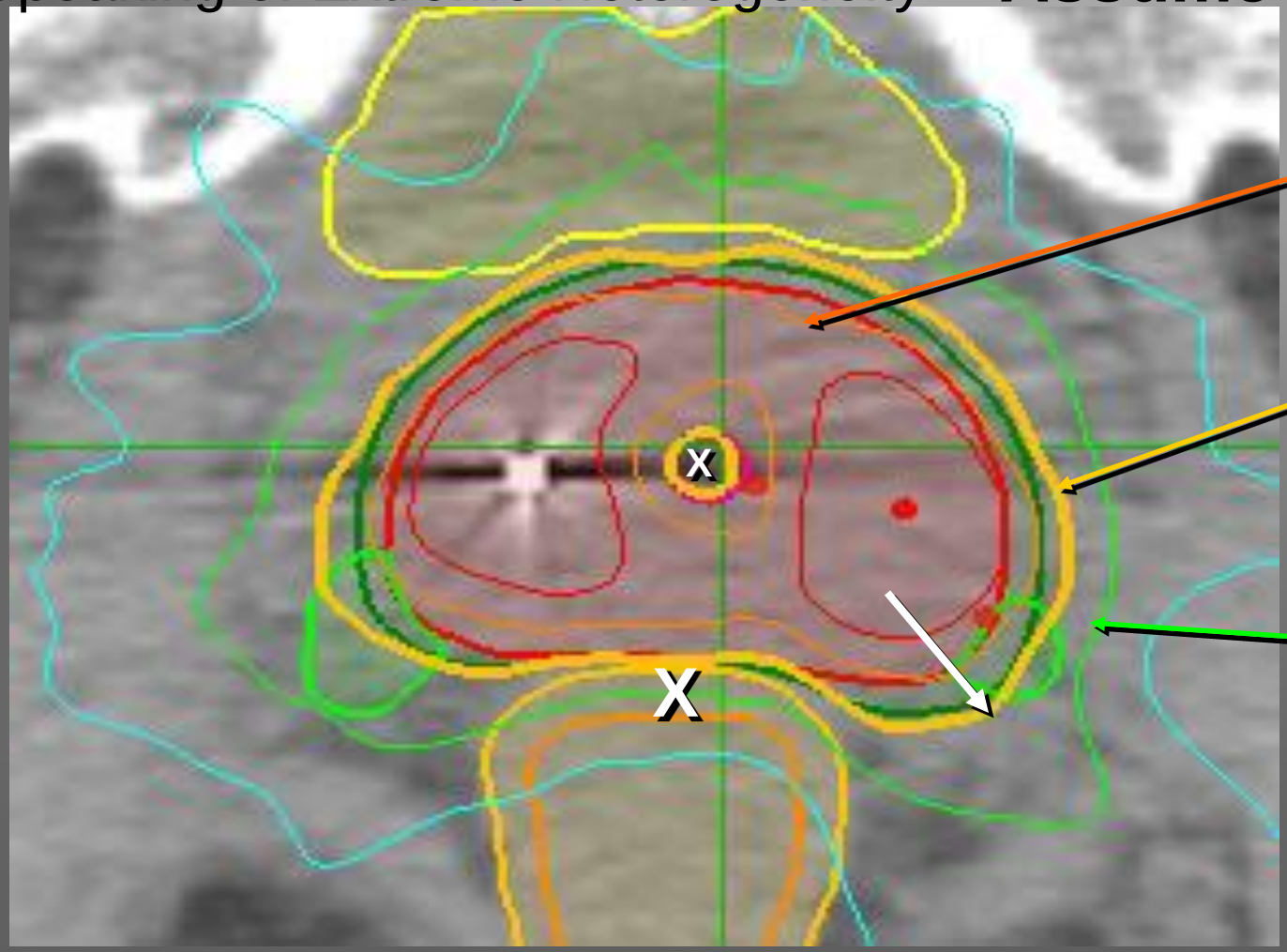
SBRT DATA

35Gy in 5f ≈ 85 Gy

Article	n	Médian f up	Dose (Gy)	Scheme	Psa free surv.
Madsen	40	41	33.5	6.5Gy*5	90% 4 years
Tang	30	12	35	7Gy*5	NP
Friedland	24	24	35	7Gy*5	NP
Bolzicco	45	20	35	7Gy*5	NP
Katz	300	30	35-36.25	7Gy*5 7.25Gy*5	4 recurences
Jabbari	20	18.3	38	9.5Gy*4	100%
Boike	15-15-15	30, 18, 12	45, 47.5, 50	5*9-9.5-10 Gy	100%

Virtual HDR® Prostate CyberKnife Radiosurgery: Intermediate–term Efficacy and Toxicity Evaluation courtesy of D. Fuller

- Speaking of Extreme Heterogeneity **Assume alpha/beta = 3**



47.5Gy/4fx;

BED = 234

(140Gy/70fx)

38Gy/4fx;

BED = 158

(94Gy/47fx)

28.5Gy/4fx;

BED = 96

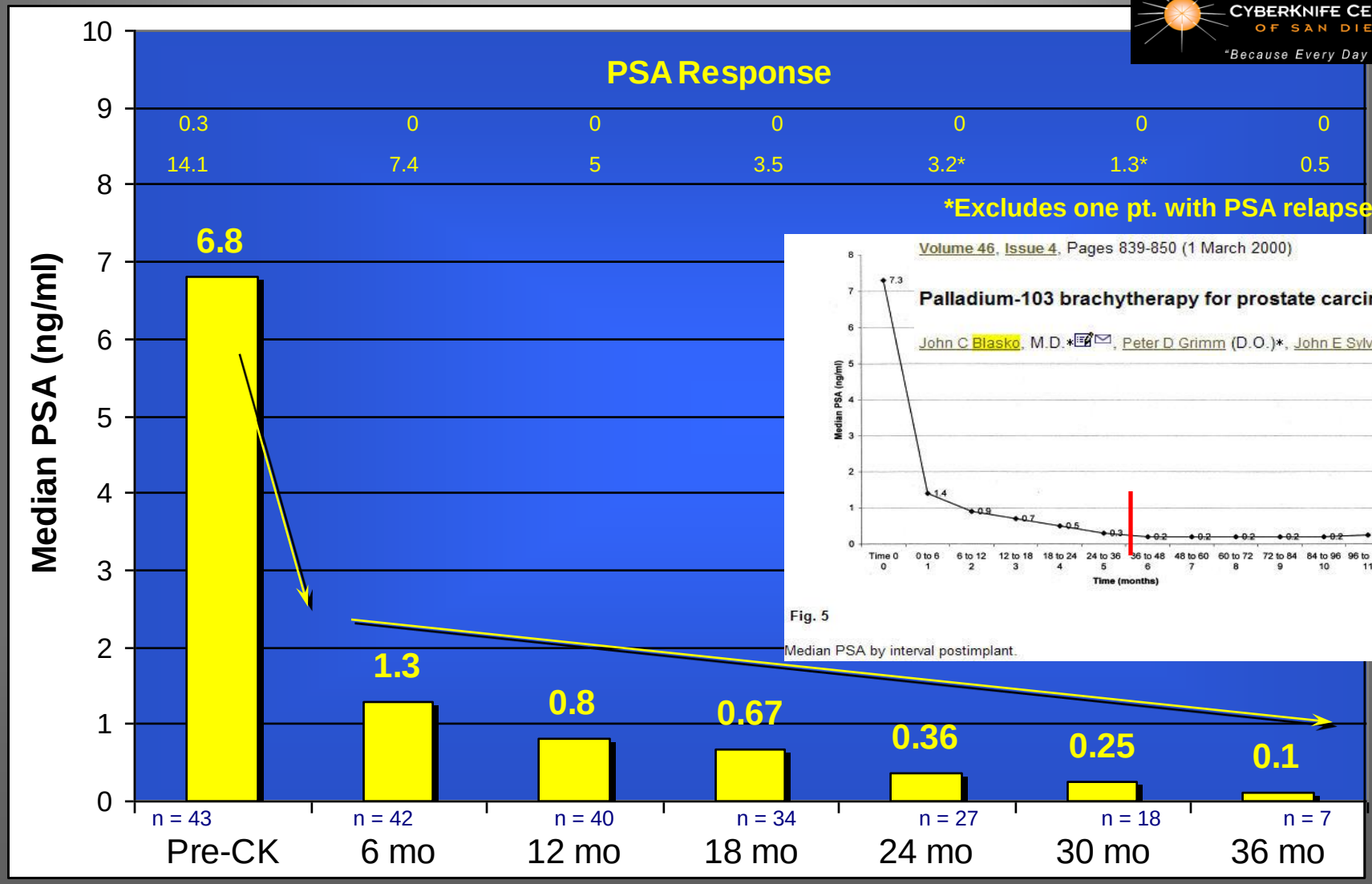
(58Gy/29fx)

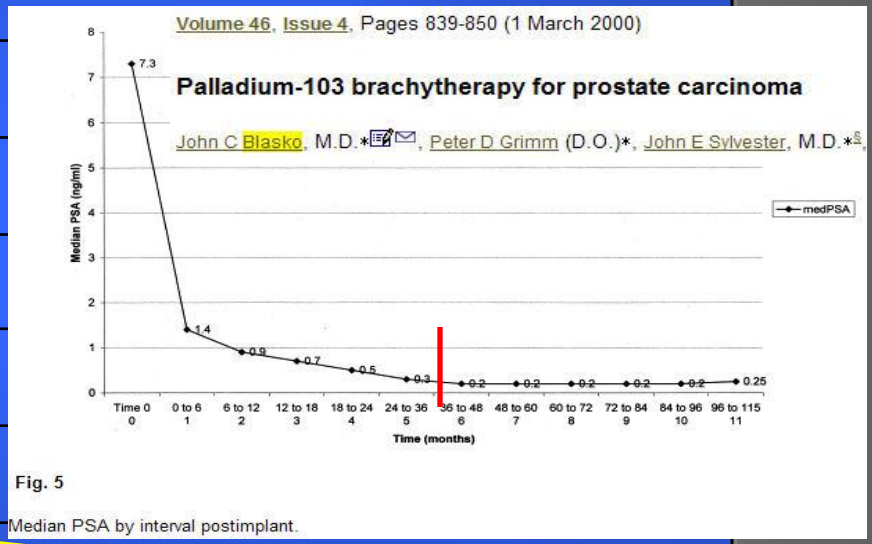
CyberKnife Centers of San Diego

"Because Every Day Counts"

Virtual HDR® Prostate CyberKnife Radiosurgery: Intermediate–term Efficacy and Toxicity Evaluation

CyberKnife Centers of San Diego
"Because Every Day Counts"





Volume 46, Issue 4, Pages 839-850 (1 March 2000)

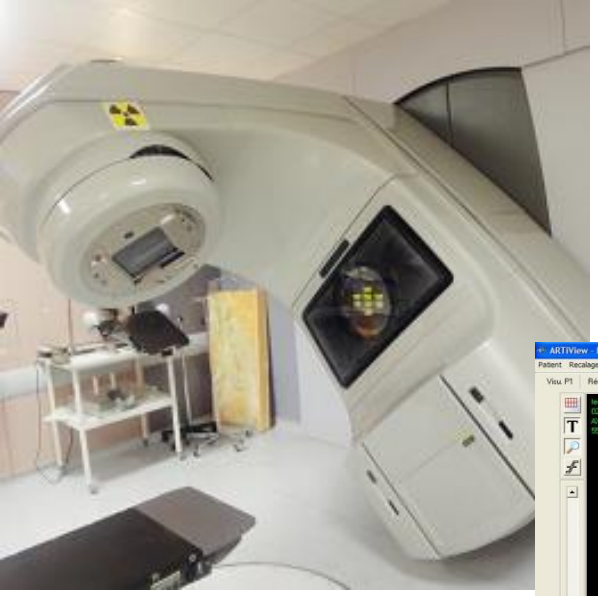
Palladium-103 brachytherapy for prostate carcinoma

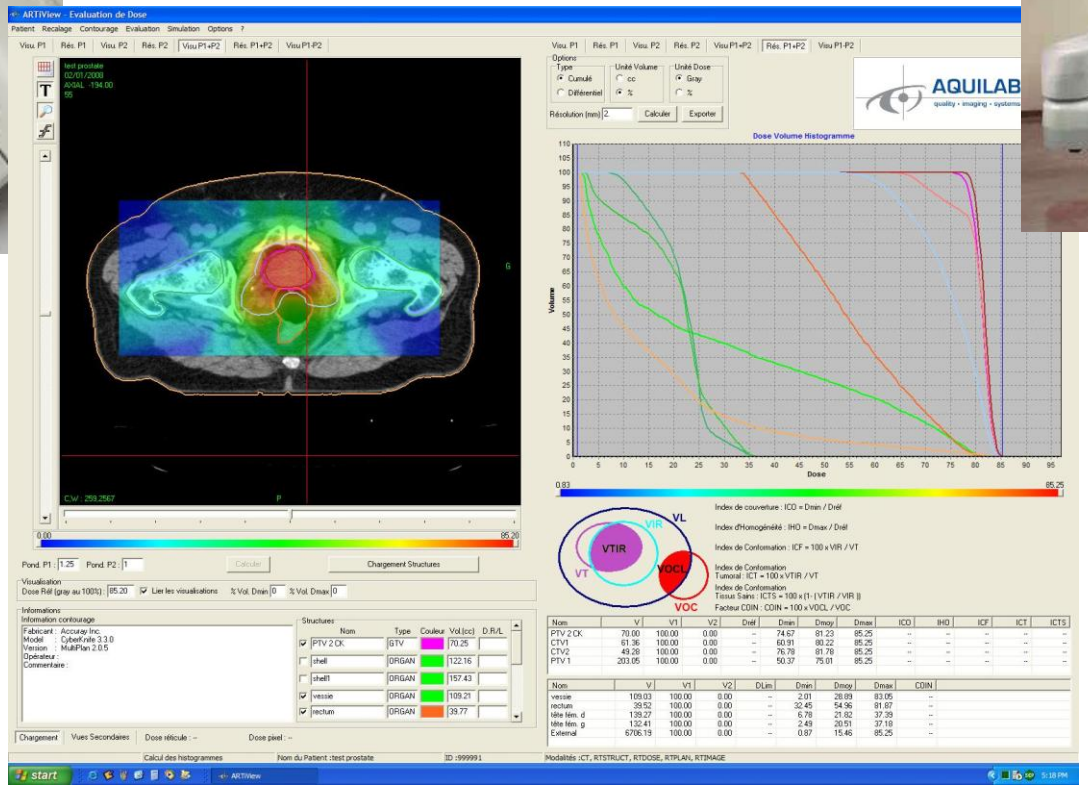
John C Blasko, M.D.*, Peter D Grimm (D.O.)*, John E Sylvester, M.D.*,

Fig. 5

Median PSA by interval postimplant.

Phase II CKNO-PRO





RT3D : 46 Gy en 23 x 2 Gy ⟷ **RTS : 18 Gy en 3 x 6 Gy**

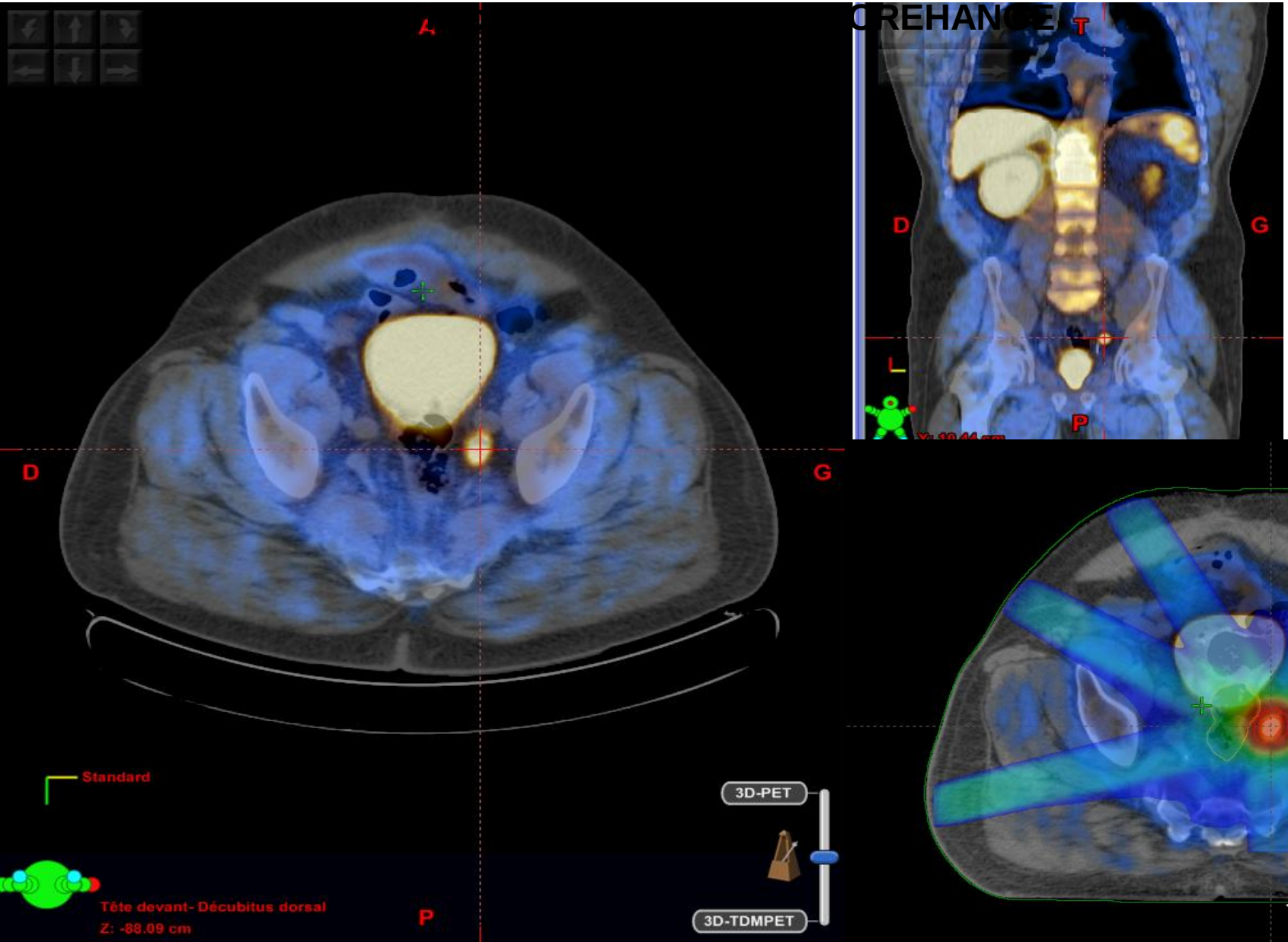
+/- IMRT

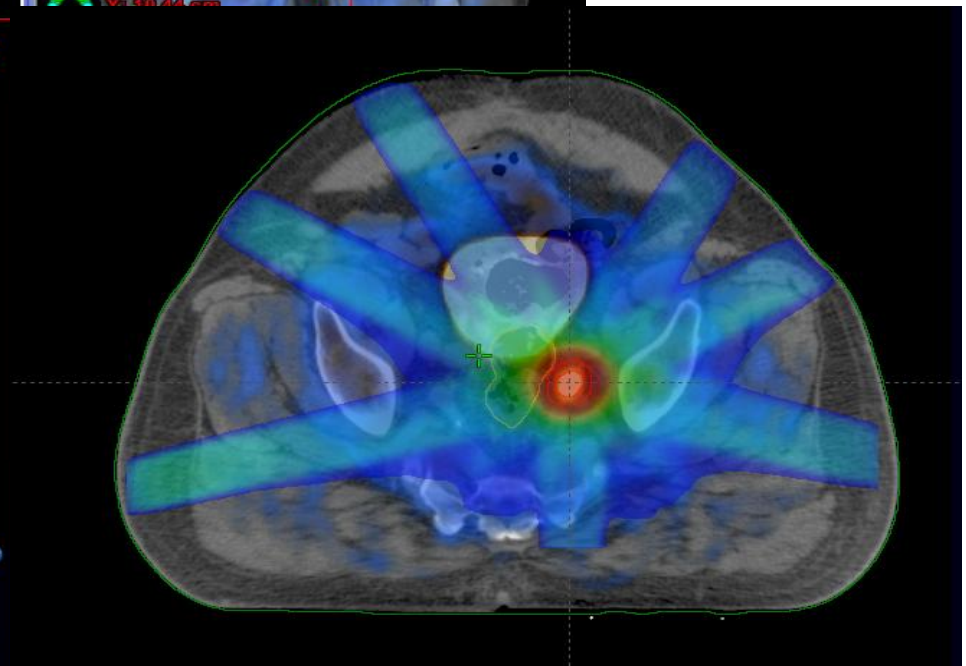
Gap : 10 days

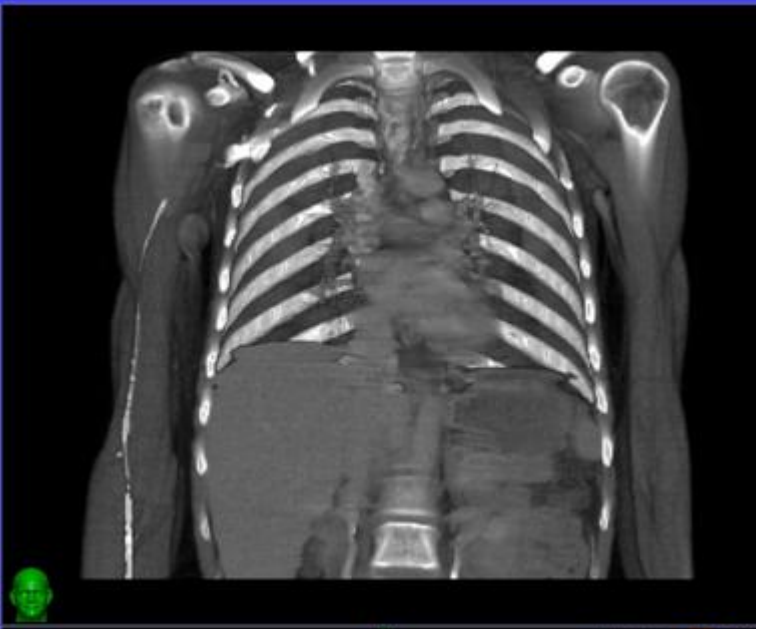
PHRC 2007: ICHOROPRO :

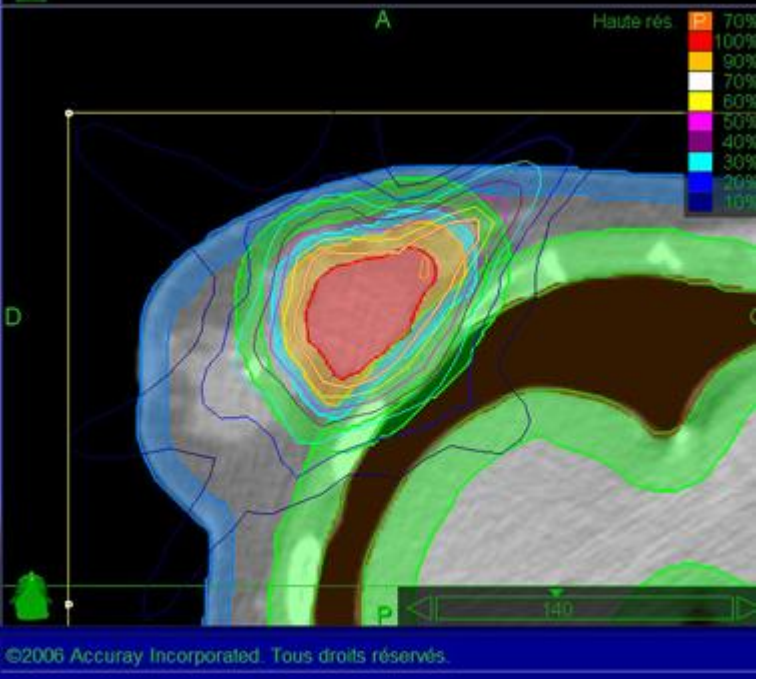
FLUOROMETHYLCHOLINE-(18F) in prostate cancer

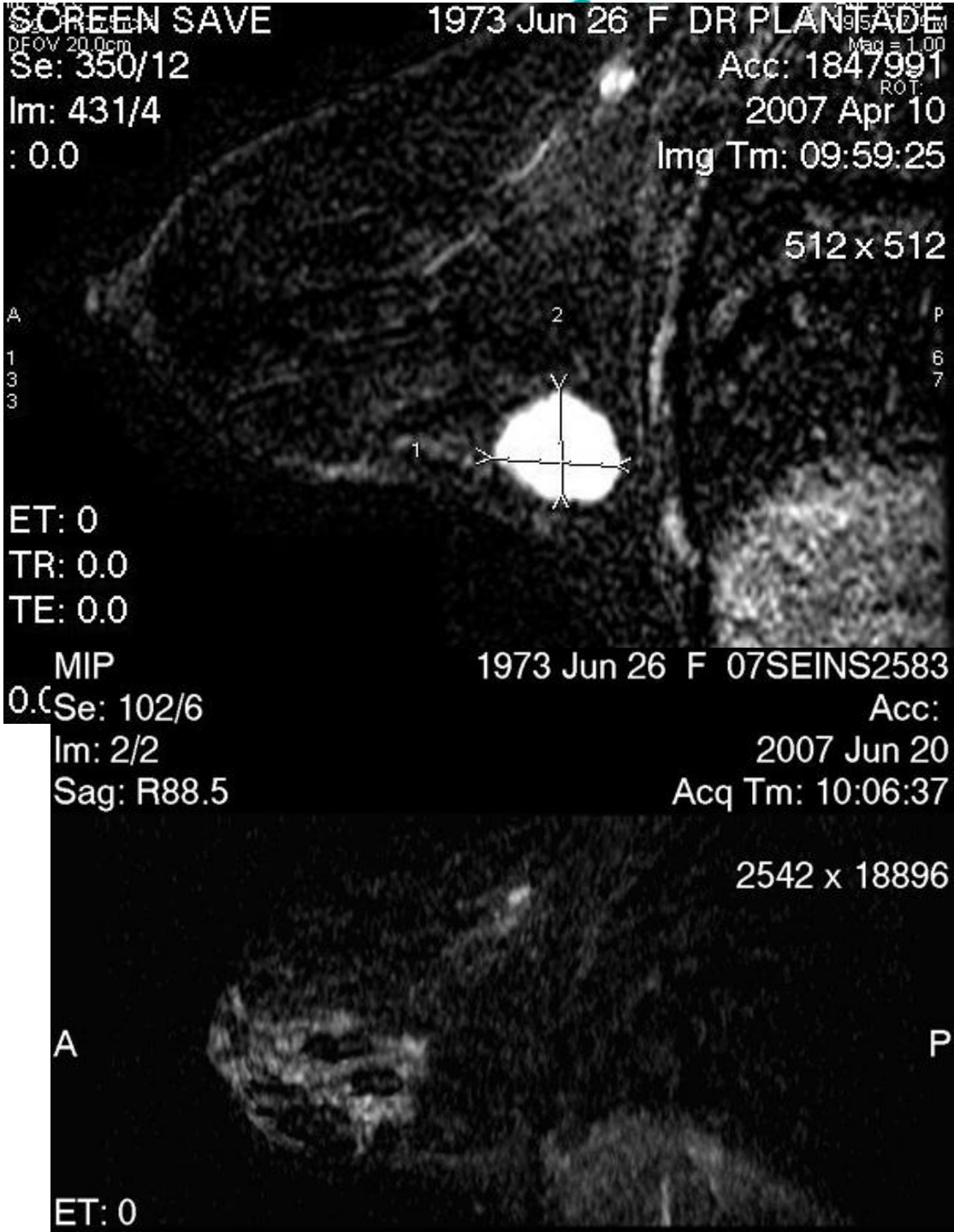
CGFL
CENTRE GEORGES
FRANÇOIS LECLERC











PY Bondiau, Nice

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Critical Reviews in Oncology/Hematology 79 (2011) 308–314

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Centre Oscar Lambret

Results and special considerations when treating elderly patients with CyberKnife®: A review of 345 cases

S. Dewas[a], C. Dewas-Vautravers[a], V. Servent[b], X. Mirabel[a], B. Prevost[a], B. Coche[a], B. Castelain[a], P. Nickers[a], E. Lartigau[a,*]

[a] Academic Radiotherapy Departement, CLCC Oscar Lambret, University Lille II, Lille, France

[b] UPCOG, Breast Unit, Departement of Medical Oncology, CLCC Oscar Lambret, University Lille II, Lille, France

Accepted 17 September 2010

Table 1
Treatment time per session as a function of the location treated and age of patient.

	Treatment time in minutes (CI = 95%)		p
	Less than 70 years	More than 70 years	
All locations combined	66.8 (62.5–71)	76.2 (69.5–82.9)	0.019
Cancer UADT	47.2 (43.8–50.6)	46.4 (38.8–53.9)	0.821
Hepatic irradiation	106.2 (98.8–114.3)	105 (95.4–114.6)	0.807
Bronchial cancer	60.3 (45.7–74.9)	68.4 (56.1–80.6)	0.405
Bone irradiation	70.6 (63.3–78)	60.3 (40.4–80.3)	0.256

CI: confidence interval.

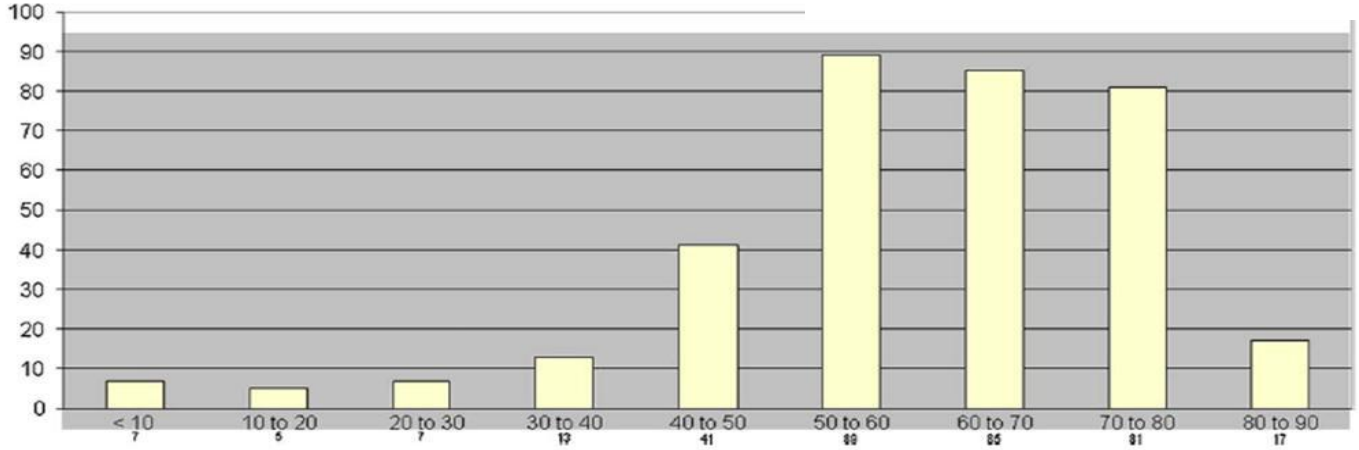


Fig. 1. Distribution of the ages of 345 patients treated by CyberKnife between June 2007 and June 2009.

Excellent tolerance in aging population

Radioresistant tumours

- Biology of High dose / fraction : **BED > 100 Gy**

- Melanoma
- Renal tumours
- Sarcomas
- …

Hindawi Publishing Corporation
Clinical and Developmental Immunology
Volume 2011, Article ID 439752, 7 pages
doi:10.1155/2011/439752

Review Article

The Confluence of Stereotactic Ablative Radiotherapy and Tumor Immunology

Steven Eric Finkelstein,[1] Robert Timmerman,[2] William H. McBride,[3] Dörthe Schaue,[3] Sarah E. Hoffe,[4] Constantine A. Mantz,[1] and George D. Wilson[5]

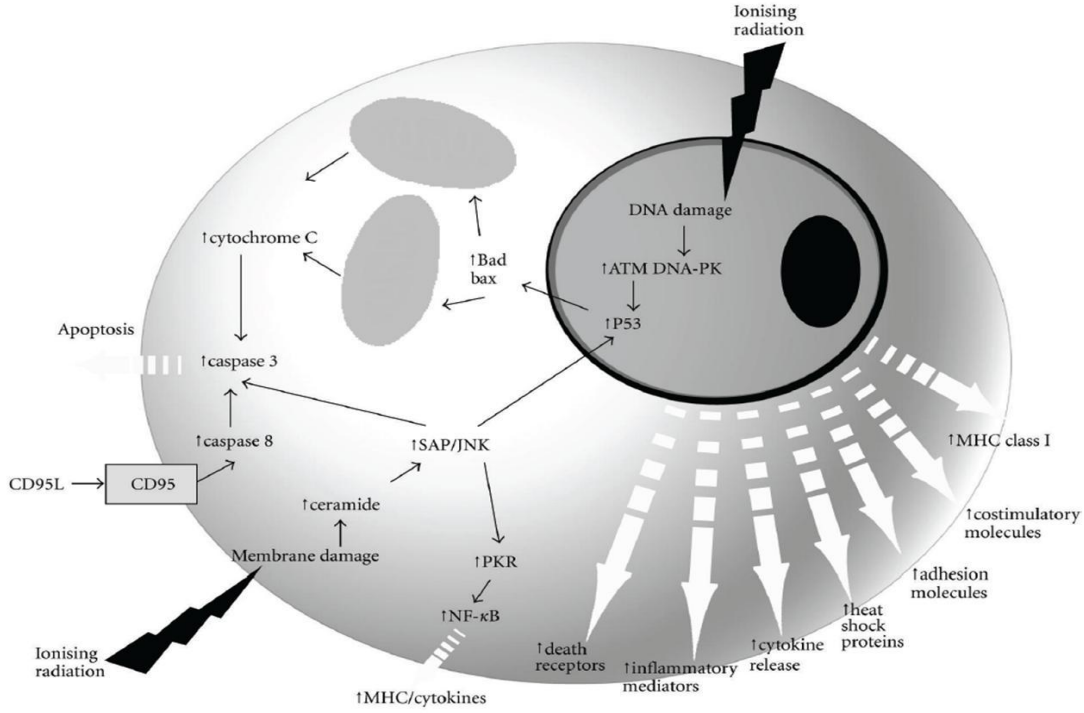
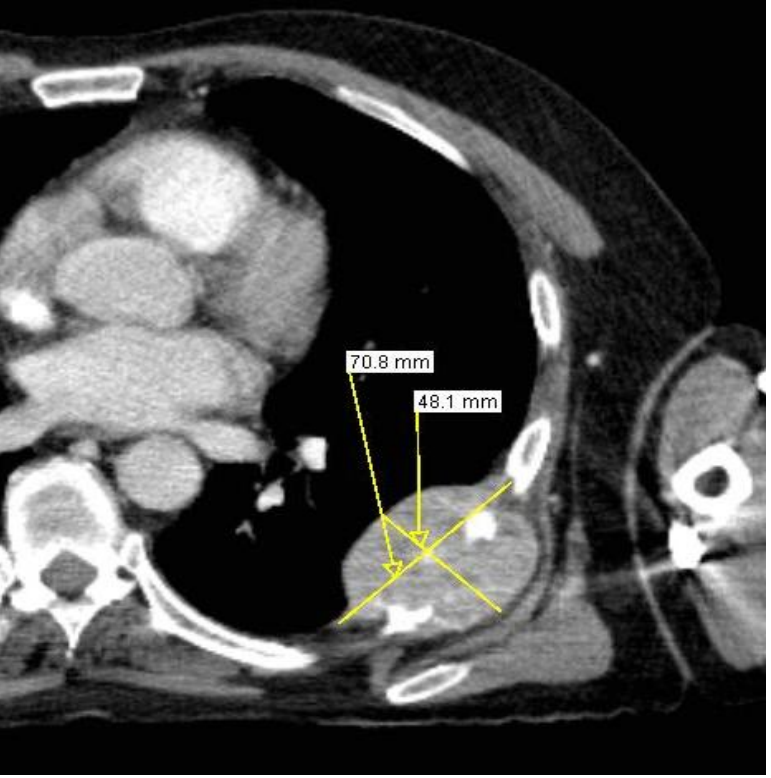
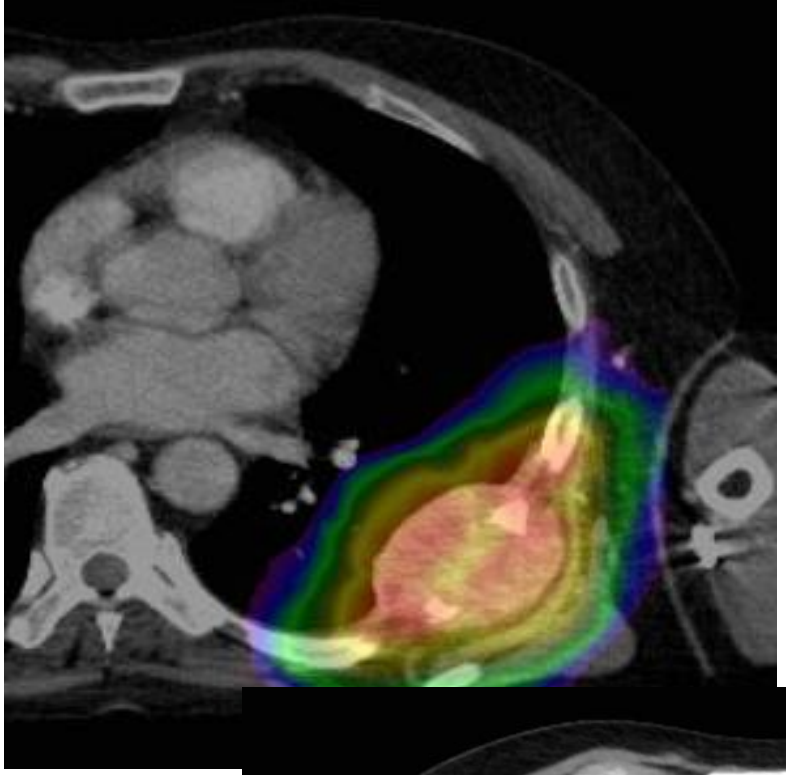


FIGURE 1: *Confluence of SABR and Immunotherapy.* Apoptosis can be initiated by SABR-induced DNA damage and upregulation of the p53 tumor suppressor gene. In addition, apoptosis can be triggered by SABR-induced damage to the cellular lipid membrane, which can induce ceramide formation and activate the SAPK/JNK signaling pathway. Thus, SAPK/JNK can upregulate PKR expression, which can induce MHC and cytokines via NF-κB. SABR can induce cellular expression of MHC Class I, adhesion molecules, costimulatory molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines, and death receptors.





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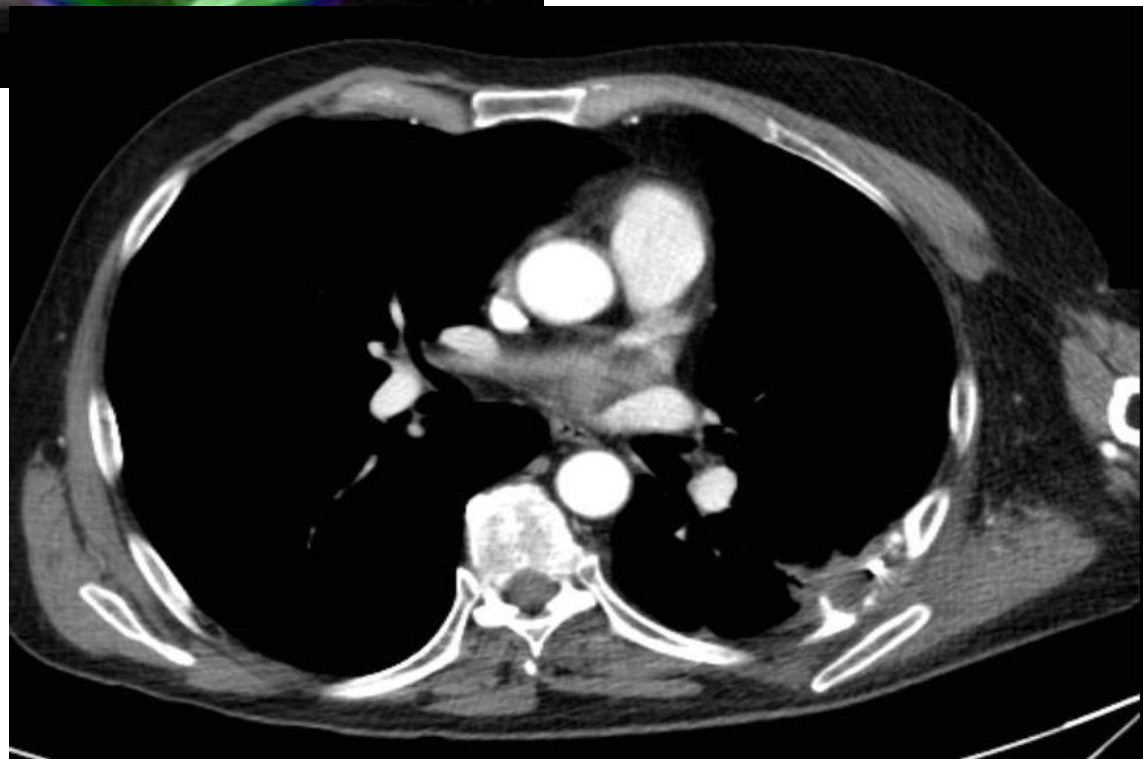

Renal metastase 3 x 15 Gy

at 3 years

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SBRT

- An enlarged role in the treatment of cancer
- Combined to targeted agents ? (lung, liver, kidney…)

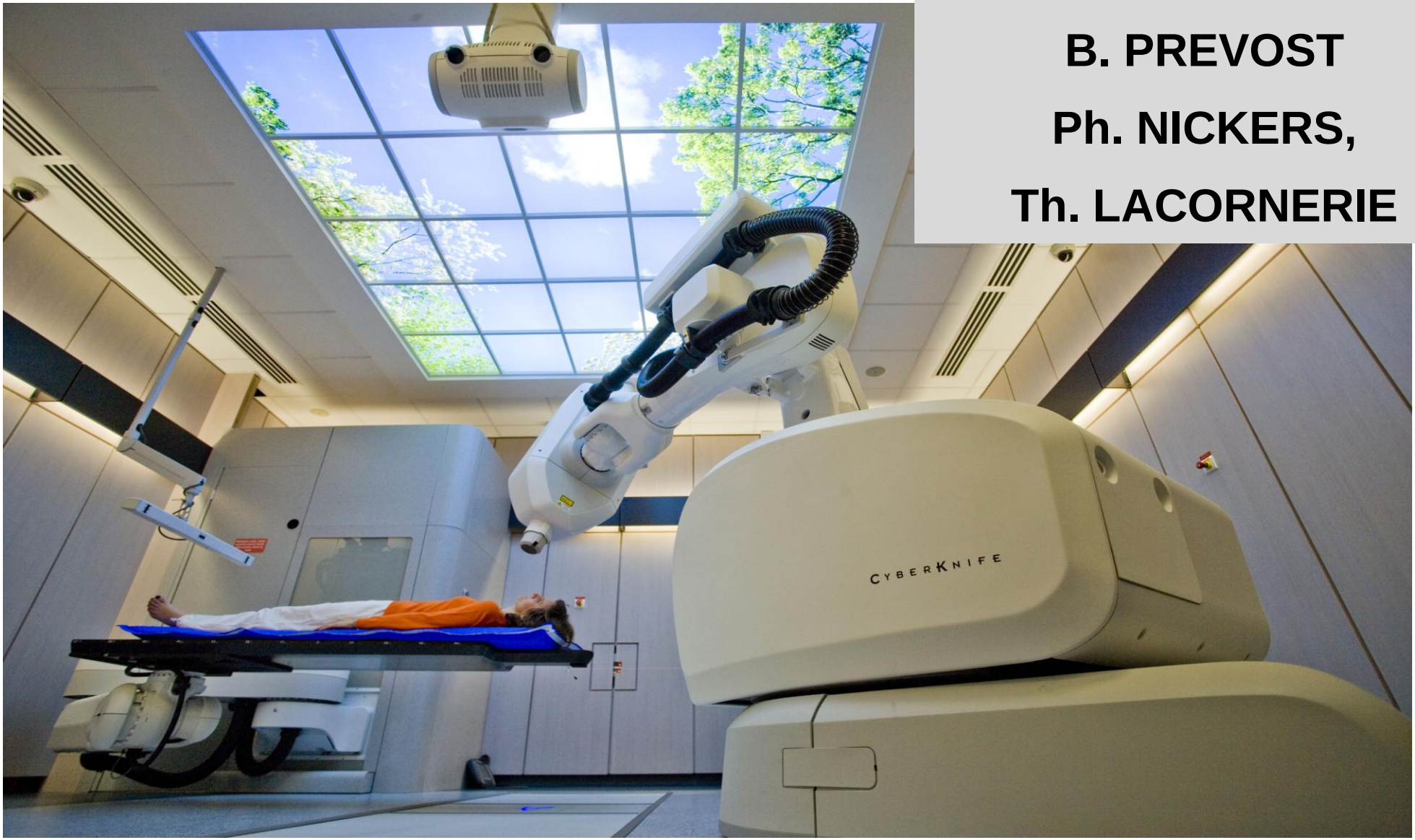
Thanks to :

X. MIRABEL,

B. PREVOST

Ph. NICKERS,

Th. LACORNERIE



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