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INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

Faire avancer la sûreté nucléaire

Les effets des rayonnements ionisants sur le système cardiovasculaire

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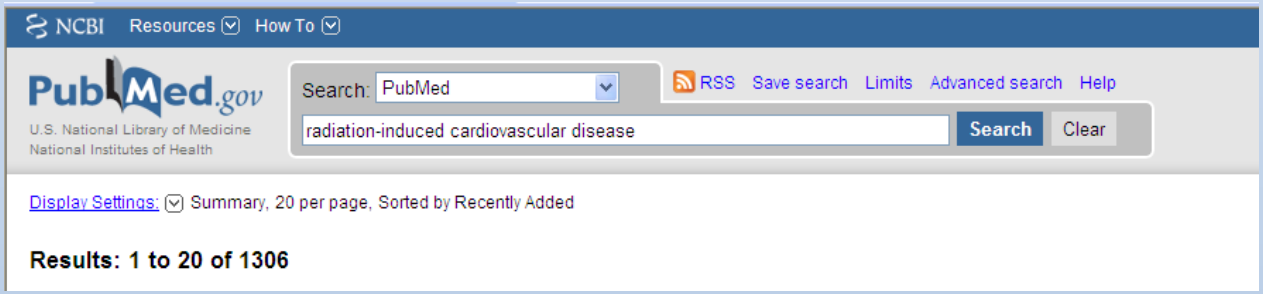
Laboratoire de Radiopathologie et de thérapies Expérimentales

IRSN, Fontenay-aux Roses

Congrès National de Radioprotection, SFRP, 21 juin 2011, Tours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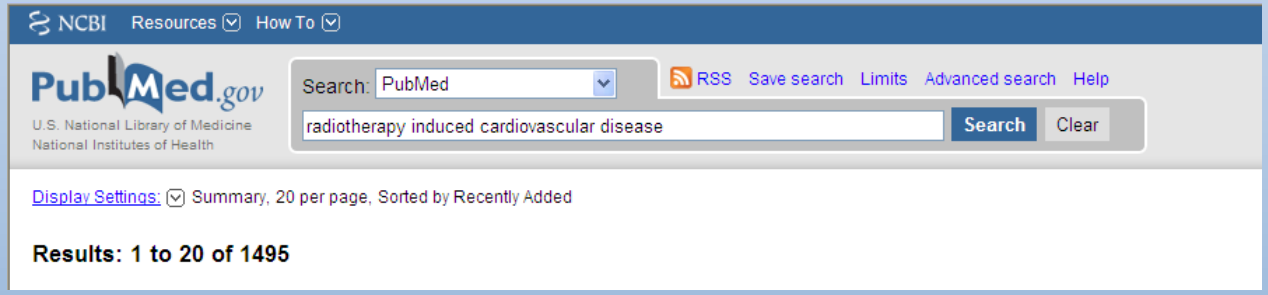
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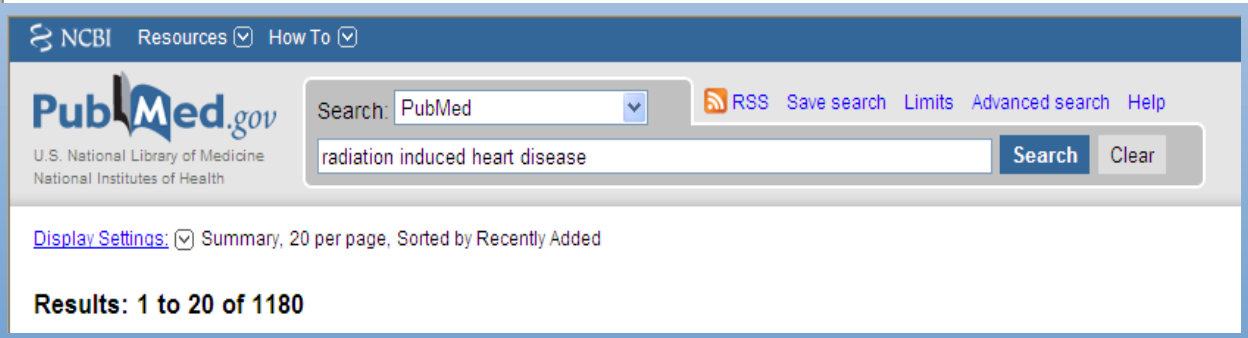
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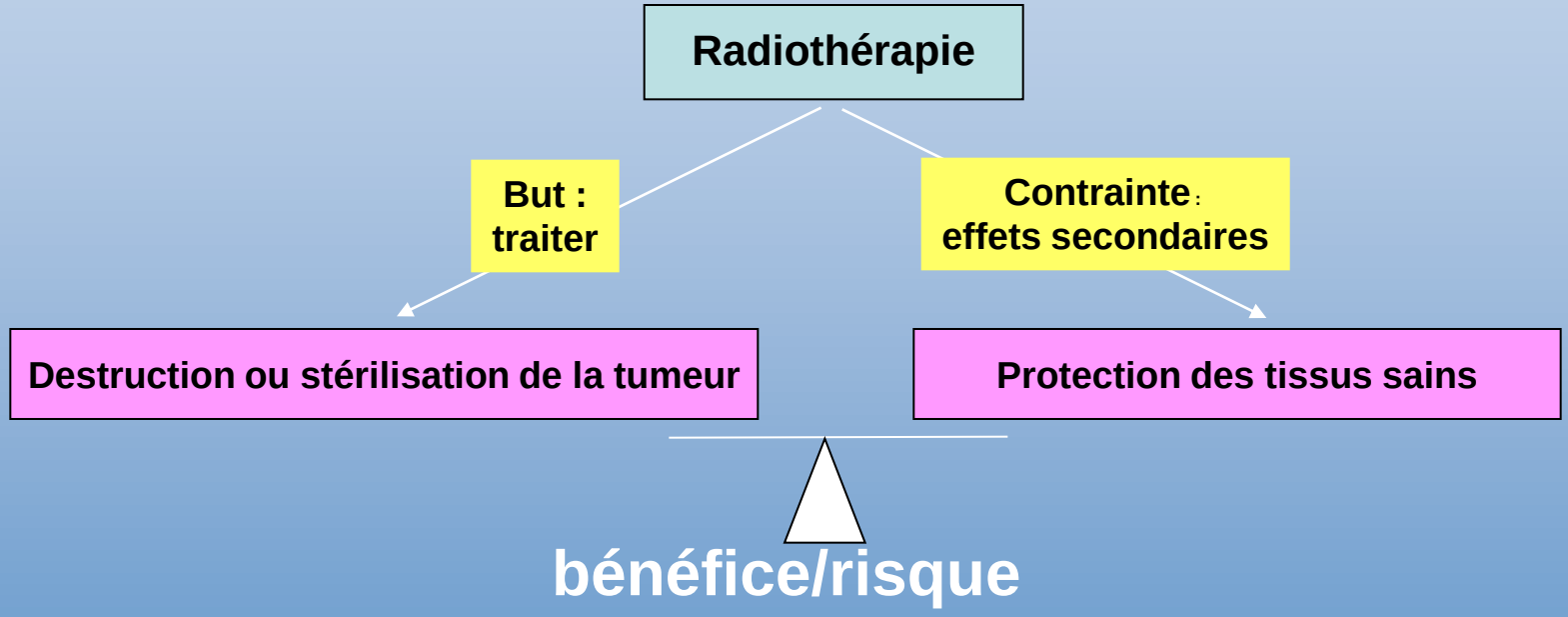
-**Radiothérapie : risque cardiovasculaire et cérébrovasculaire**

-**Effets des rayonnements ionisants et pathologies cardiovasculaires aux fortes doses**

aspects physiopathologiques et mécanismes moléculaires

-**Effets des rayonnements et pathologies cardiovasculaires : cas des faibles doses**

Radiothérapie et risque cardiovasculaire



Radiothérapie : notion d'organe à risque (OAR)

Cancer	OAR
Prostate	Rectum, Véssie
Sein	Poumon, cœur, foie, moelle épinière …
Tête et cou	Larynx, Parotides, Thyroide

Le **cœur** est un OAR des RT des cancers :
sein
lymphome
poumon
œsophage
Estomac
thymome

Source : Guide des procédures de radiothérapie externe 2007, Cancer/Radiothérapie 12 (2008) 143-413

Tableau III – Tableau regroupant les doses de tolérance (HDV, dose maximale, dose moyenne) ayant fait l'objet d'un consensus fort ou relatif en 2007.

Ces niveaux de dose peuvent éventuellement être dépassés sous réserve d'une justification liée au contrôle local et à la survie du patient, après information et accord de celui-ci. Ces dépassements sont notamment possibles lorsqu'ils concernent des organes à risque dont les lésions radiques n'ont pas de conséquences vitales.

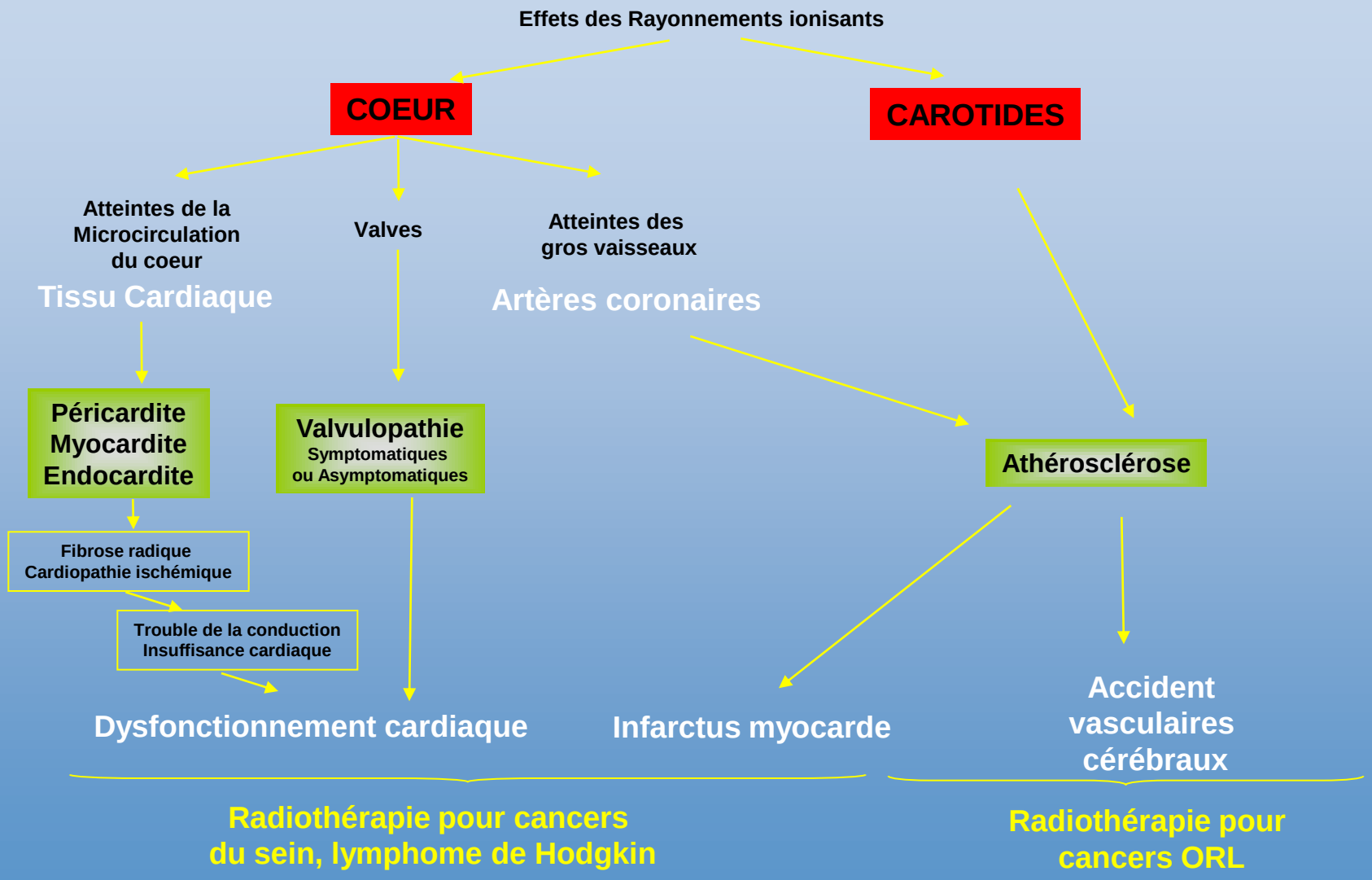
Organe sain (organe à risque)	Dose de tolérance
Parotide controlatérale	V26 ≤ 50% Dose moyenne < 30 Gy
Tronc cérébral	Dose maximale de 50 Gy
Articulation temporo-mandibulaire, notamment controlatérale	Dose maximale de 65 Gy
Moelle épinière	Dose maximale de 45 Gy
Larynx	Dose maximale de 20 Gy
Chiasma	Dose maximale de 54 Gy
Conduit auditif, oreille moyenne et interne	Dose maximale de 50-55 Gy
Œil	Dose moyenne < 35 Gy
Poumon sain	V20 ≤ 35 % V30 ≤ 20 %
Plexus brachial	Dose maximale de 55 Gy
Œsophage	Dose maximale de 40 Gy sur une hauteur de 15 cm
Foie	V30 ≤ 50% Dose <26 Gy dans le foie total
Cœur	Dose maximale de 35 Gy dans l'ensemble du cœur
Rein	Dose maximale de 20 Gy dans un volume cumulé équivalent à un rein entier fonctionnellement normal
Intestin grêle	Dose maximale de 50 Gy Dose maximale de 40 Gy sur un grand volume
Estomac, duodénum	Dose maximale de 45 Gy Dose maximale de 54 Gy dans un petit volume
Vessie	V60 ≤ 50% V70 ≤ 25%.
Cols, têtes fémorales, grand trochanter	V 50 ≤ 10 %.
Rectum (paroi rectale)	V60 ≤ 50 %. V70 ≤ 25 % V74 ≤ 5 %

Source : Guide des procédures de radiothérapie externe 2007, Cancer/Radiothérapie 12 (2008) 143-413

Le risque cardio-vasculaire et cerebro-vasculaire quels cancers ?

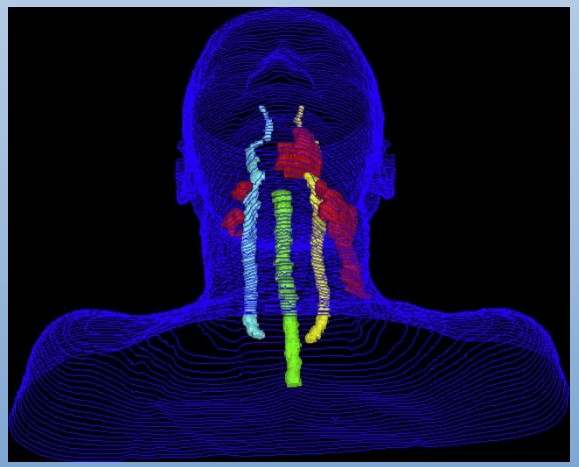
Cancer du sein
Lymphome de hodgkin
Cancer tête et cou

Radiothérapie et risque cardio/cérébro-vasculaire



Le cas des carotides !!

rouge
volume tumoral macroscopique
bleu jaune
carotides



Radiothérapie et risque cardiovasculaires et cérébro-vasculaires

(Cancer du sein, Lymphome de Hodgkin et cancer tête et cou)

Quels ont les facteurs pouvant influencer ce risque ?
Age, temps de suivi, tabac, …

Quelle est la dose ou le seuil de dose qui détermine le risque ?

Quelles sont les structures à risques ?

Apport des nouvelles techniques de radiothérapie ?

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

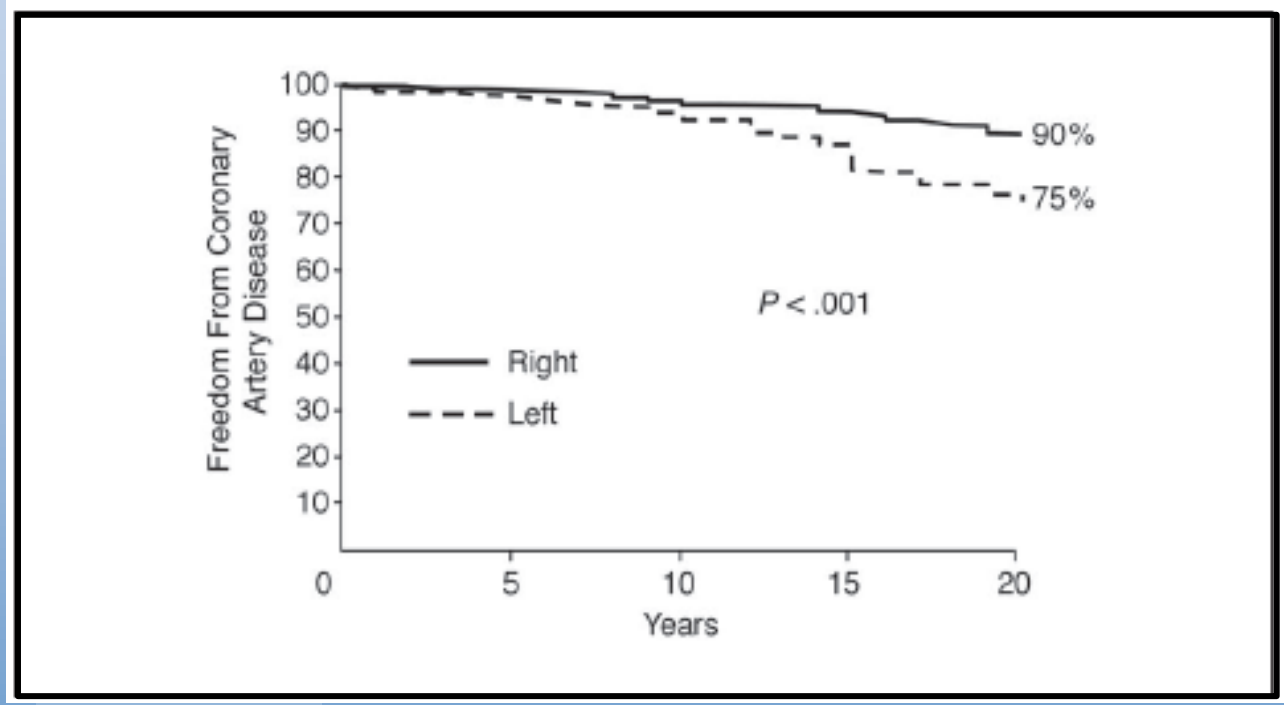
Lancet 2005

Méta-analyse : 42 000 patients, 78 essais randomisés (avec ou sans RT)

Mortality before recurrence, from causes other than breast cancer					
By cause					
Circulatory disease	1510	77·6	345·4	1·25 (0·06)	0·00003
Heart disease, etc§	1106	60·7	252·7	1·27 (0·07)	0·0001
Stroke	345	9·1	80·9	1·12 (0·12)	0·3
Pulmonary embolism	59	7·8	11·8	1·94 (0·41)	0·02
Other specified cause	1455	6·4	335·8	1·02 (0·06)	0·7
Lung cancer	156	21·7	37·5	1·78 (0·22)	0·0004
Oesophagus cancer	23	4·9	5·6	2·40 (0·68)	0·04
Leukaemia	31	2·4	7·0	1·40 (0·45)	0·4
Soft-tissue sarcoma	7	1·3	1·7	2·13 (1·14)	0·3
Respiratory disease (460–519, 786)	241	−1·0	55·5	0·98 (0·13)	0·9
Other known cause	997	−22·9	228·5	0·90 (0·06)	0·1
Unspecified cause, not breast cancer	701	7·8	159·4	1·05 (0·08)	0·5

Cancer du sein et risque cardiovasculaire

Le risque dépend de la localisation du cancer



961 patientes
(USA)
1977-1994
Coronaropathie

Harris *et al.*, JNCI, 2006

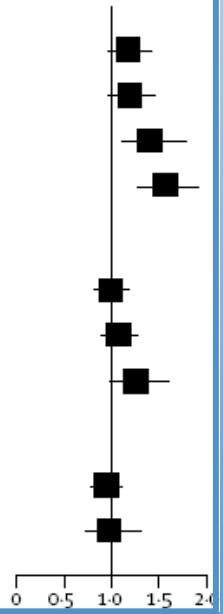
Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300 000 women in US SEER cancer registries

Sarah C Darby, Paul McGale, Carolyn W Taylor, Richard Peto

Lancet Oncology, 2005

115165 patientes RT (USA)
Cohorte SEER
(Surveillance Epidemiology end Results)
1973-2001

Years from breast cancer diagnosis to cardiac death	Radiotherapy	
	Cardiac deaths left/right	Cardiac mortality ratio, left-sided vs right-sided (95% CI)
Diagnosed 1973–82		
<5 years	230/180	1·19 (0·98–1·45)
5–9	189/145	1·21 (0·97–1·50)
10–14	157/106	1·42 (1·11–1·82)
⩾15	234/145	1·58 (1·29–1·95)
Diagnosed 1983–92		
<5 years	245/227	1·00 (0·84–1·20)
5–9	249/218	1·08 (0·90–1·29)
⩾10	144/108	1·27 (0·99–1·63)
Diagnosed 1993–2001		
<5 years	225/226	0·95 (0·79–1·14)
5–9	83/79	0·99 (0·73–1·35)



Le risque dépend
- de la période de traitement
- du temps de suivi

4414 patientes (NL)
1970-1986, survivantes à >10 ans
Infarctus

	no RT			RT
Risk factor	HR† (95% CI)	No. of patients at risk	No. of events	HR† (95% CI)
Smoking§				
No	1.00 (ref.)	2072	113	1.34 (0.94 to 1.91)
Yes	1.36 (0.69 to 2.68)	737	61	3.04 (2.03 to 4.55)
Hypercholesterolemia				
No	1.00 (ref.)	2780	134	1.59 (1.13 to 2.24)
Yes	3.11 (1.78 to 5.42)	315	57	4.62 (3.06 to 6.98)
Hypertension				
No	1.00 (ref.)	2302	95	1.92 (1.22 to 3.01)
Yes	2.49 (1.49 to 4.16)	793	96	3.31 (2.09 to 5.24)
Diabetes mellitus				
No	1.00 (ref.)	2843	160	1.81 (1.29 to 2.53)
Yes	2.01 (1.15 to 3.53)	252	31	1.87 (1.17 to 3.00)
History of IHD				
No	1.00 (ref.)	3044	181	1.56 (1.16 to 2.11)
Yes	1.53 (0.54 to 4.32)	51	10	2.31 (1.15 to 4.65)

Hooning *et al.*, JNCI, 2007

La radiothérapie potentialise le risque cardio-vasculaire lié au tabac

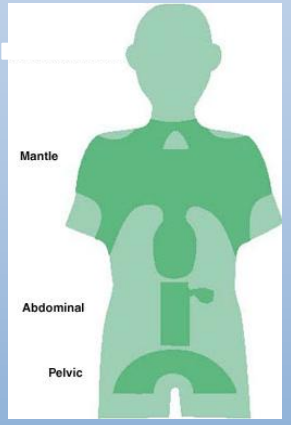
Lymphome de Hodgkin et risque cardio et cérébrovasculaire

1- Augmentation du risque en fonction du champs irradié

Treatment modality	Radiotherapy without anthracyclines (n = 3590; median follow-up = 12.3 y) No. of deaths	SMR (95% CI)	P‡
Radiotherapy			
Total nodal (n = 290)	19	9.0 (5.4 to 14.1)	<.001
Subtotal nodal, no total nodal (n = 134)	5	2.6 (0.9 to 6.2)	.09
Mantle, no total or subtotal nodal (n = 1969)	45	3.2 (2.3 to 4.3)	<.001
Other supradiaphragmatic, no mantle or total or subtotal nodal (n = 1069)	19	1.9 (1.2 to 3.0)	.01
Unknown field, no known supradiaphragmatic (n = 1325)	18	2.3 (1.4 to 3.7)	.002
Infradiaphragmatic only (n = 249)	2	0.5 (0.1 to 1.9)	.56

3%

Swerdlow *et al.*, JNCI, 2007



7033 patients (UK)
1967-2000
Mortalité cardiaque

2- Augmentation du risque en fonction du temps de suivi

Time since start of first treatment (y)	Supradiaphragmatic radiotherapy No. of deaths	SMR (95% CI)	P†
<1	5	1.8 (0.6 to 4.2)	.31
1–9	49	2.4 (1.8 to 3.2)	<.001
10–19	46	3.6 (2.7 to 4.9)	<.001
≥20	13	4.3 (2.3 to 7.4)	<.001
Total	113	2.9 (2.4 to 3.5)	<.001

3- Augmentation du risque en fonction de l'âge

Age at first treatment (y)	Supradiaphragmatic radiotherapy No. of deaths	SMR (95% CI)	P†
<35	34	10.1 (7.0 to 14.1)	<.001
35–54	43	2.9 (2.1 to 3.9)	<.001
≥55	36	1.8 (1.2 to 2.4)	.003
Total	113	2.9 (2.4 to 3.5)	<.001

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Lymphome de Hodgkin et risque cardio et cérébrovasculaire

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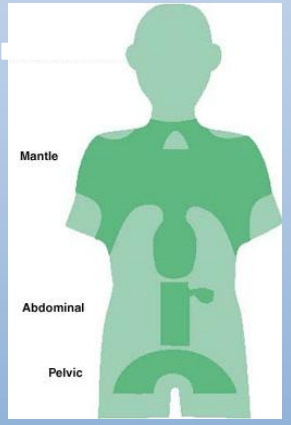
Swerdlow *et al.*, JNCI, 2007



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≥55	36	1.8 (1.2 to 2.4)	.003
Total	113	2.9 (2.4 to 3.5)	<.001

4- Augmentation du risque cérébrovasculaire

Group	Total No.	Experienced Late-Occurring Stroke No.	%	Relative Risk	95% CI	P
Siblings	3,846	9	0.23	1.00	Reference	—
HD + mantle RT patients	1,386*	24	1.73	5.62	2.59 to 12.25	< .0001

1926 patients (USA)
1970-1986
AVC

Bowers *et al.*, J Clin Oncol, 2005

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Cancer tête-et-cou et risque cérébrovasculaire

1- L'hypertension et le diabète augmentent le risque d'AVC après radiothérapie

Risk Factor	Observed Strokes	Expected Strokes	RR	95% CI	AER (/1,000 patients/yr)
Overall	14	2.50	5.6	3.1-9.4	3.8
Hypertension					
No	8	1.87	4.3	1.8-8.4	2.6
Yes	6	0.48	12.5	4.6-27.2	11.6
DM					
No	12	2.07	5.8	3.0-10.1	3.8
Yes	2	0.17	12.1	1.5-43.5	17.7

Dorresteijn *et al.*, J Clin Oncol, 2002

367 patients (NL)
(1977-1998)
<60 ans âge médian: 49.3 ans

RT: 50-66 Gy ± chirurgie
Dose carotide: 95-100%

2- Le risque augmente avec le temps de suivi et l'âge au moment de la radiothérapie

	Person-Years	Observed Cases	Expected Cases	RR	95% CI	AER/1,000 Patients/yr*
Follow-up time						
0-9 years	2,313	6	1.63	3.7	1.3-8.0	1.9
> 10 years	514	8	0.79	10.1	4.4-20.0	14.0
Age at RT						
< 50 years	1,659	5	0.51	9.8	3.2-22.9	2.7
> 50 years	1,351	9	1.99	4.5	2.1-8.6	5.2

A partir de quelle dose a t'on un risque ?

VOLUME 28 · NUMBER 8 · MARCH 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Role of Cancer Treatment in Long-Term Overall and Cardiovascular Mortality After Childhood Cancer

Markhaba Tukenova, Catherine Guibout, Odile Oberlin, Françoise Doyon, Abdeddahir Mousannif, Nadia Haddy, Sylvie Guérin, Hélène Pacquement, Albertine Aouba, Mike Hawkins, Dave Winter, Jean Bourhis, Dimitri Lefkopoulos, Ibrahima Diallo, and Florent de Vathaire

	No. of Patients	No. of Deaths	Mortality		Risk		
			SMR*	95% CI	RR†	95% CI	*P*
Mean radiation dose to the heart, Gy							
None	1,252	1	1.1	0.1 to 7.4	1‡		
< 1	1,243	4	2.8	1.1 to 7.6	3.0	0.3 to 28.0	
1-4.9	508	1	2.4	0.3 to 17.5	2.5	0.2 to 41.5	
5-14.9	421	4	13.7	5.1 to 36.4	12.5	1.4 to 116.1	
≥ 15	541	11	33.3	18.4 to 60.1	25.1	3.0 to 209.5	< .01§

Doses moyenne au cœur > 5 Gy est associée à un risque de mortalité cardiaque

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JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Long-Term Overall and Cardiovascular Mortality After Childhood Cancer: The Problem of Retrospective Estimated Radiation Doses

TO THE EDITOR: Tukenova et al[1] are to be congratulated for their recently reported retrospective analysis of 4,122 long-term survivors of malignancies in childhood and adolescence. However, we would like to make some comments regarding the method of retrospective dose calculation and the authors' conclusion on dose-effect relationships in radiation-associated heart toxicity.

Current available reports on cardiac late toxicity in children and adolescents showed little or no cardiac diseases after normofractionated radiotherapy with doses up to 25 Gy (single doses ≤ 2 Gy; median follow-up, 1.3 to 14.3 years). For irradiation with doses exceeding 25 Gy (single doses ≤ 2 to 3.3 Gy), some studies reveal higher rates of cardiac dysfunction (for review, see Bölling et al[2]). However, the median follow-up of these collectives was less than 15 years for most of the studies. Therefore, it cannot be excluded that further cardiac late sequelae may arise after a longer period of time.

The study of Tukenova et al[1] showed late cardiac mortality after much lower doses of 5 Gy to the heart after a long period of follow-up (average, 27 years). The authors refer to retrospective dose estimations that were based on sex, age, and size of the patients without further details on patients' anatomic properties in most cases. The treatment period started during World War II (1942) and ended in 1986. The radiation modalities showed a large heterogeneity and included soft x-rays, gamma-radiation from cobalt machines, and megavoltage x-rays. The doses were estimated in six points 13 to 83 cm from the central point of the radiation field, and the mean dose was assumed to reflect the cardiac dose. It should be stressed that this method cannot be compared with detailed dose calculations that have become standard in modern computed tomography–based three-dimensional radiotherapy treatment planning. Furthermore, it has to be assumed that some of the described six points with dose estimation were located outside of the radiation field, leading to relative low mean doses with some potential high maximum doses within the heart. Therefore, it should be discussed whether the mean dose really reflects the correct dose to the heart or whether the maximum dose to the heart would be more interesting.

Cardiac late sequelae after radiation doses as low as 5 Gy have also been postulated in adults. In a report regarding Japanese atomic bomb survivors,[3] significant cardiac diseases were observed after a follow-up of more than 20 years in survivors who had received a total heart single dose of 1 to 2 Gy. However, the comparison of results of atomic bomb survivors with children treated with radiotherapy may include a bias. Other reports on patients with peptic ulcer disease[4] or patients with breast cancer,[5] who had partial heart irradiation with doses of 16 to 34 Gy[4] or at least 40 Gy[5] with a median heart dose of approximately 2 Gy, also showed significantly higher heart failure rates. For these reports, as for the report of Tukenova et al,[1] whether it was the quite low dose (approximately 1 to 2 Gy) to the main volume of the heart muscle that caused the damage to the heart or the relatively high dose to a small volume of the heart is open to speculation.

A correlation of the dose to a particular region and damage to the corresponding cardiac structures has rarely been attempted because of a lack of three-dimensional computed tomography data sets in original reports. Because of the necessity of detailed organ at risk delineation in radiotherapy treatment planning, such detailed analyses will only be possible in a prospective setting.

These comments are not meant to diminish the significant effort of Tukenova et al[1] in evaluating cardiac mortality after malignancies in childhood and adolescence. However, the assumption of a critical dose of 5 Gy to the heart should not be transferred into modern clinical practice without knowledge of the potential restrictions in retrospective dose calculations and the difference between mean and maximum doses to the heart.

Tobias Bölling and Normann Willich
University Hospital of Münster, Münster, Germany

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2010.28.6872; published online ahead of print at www.jco.org on June 21, 2010

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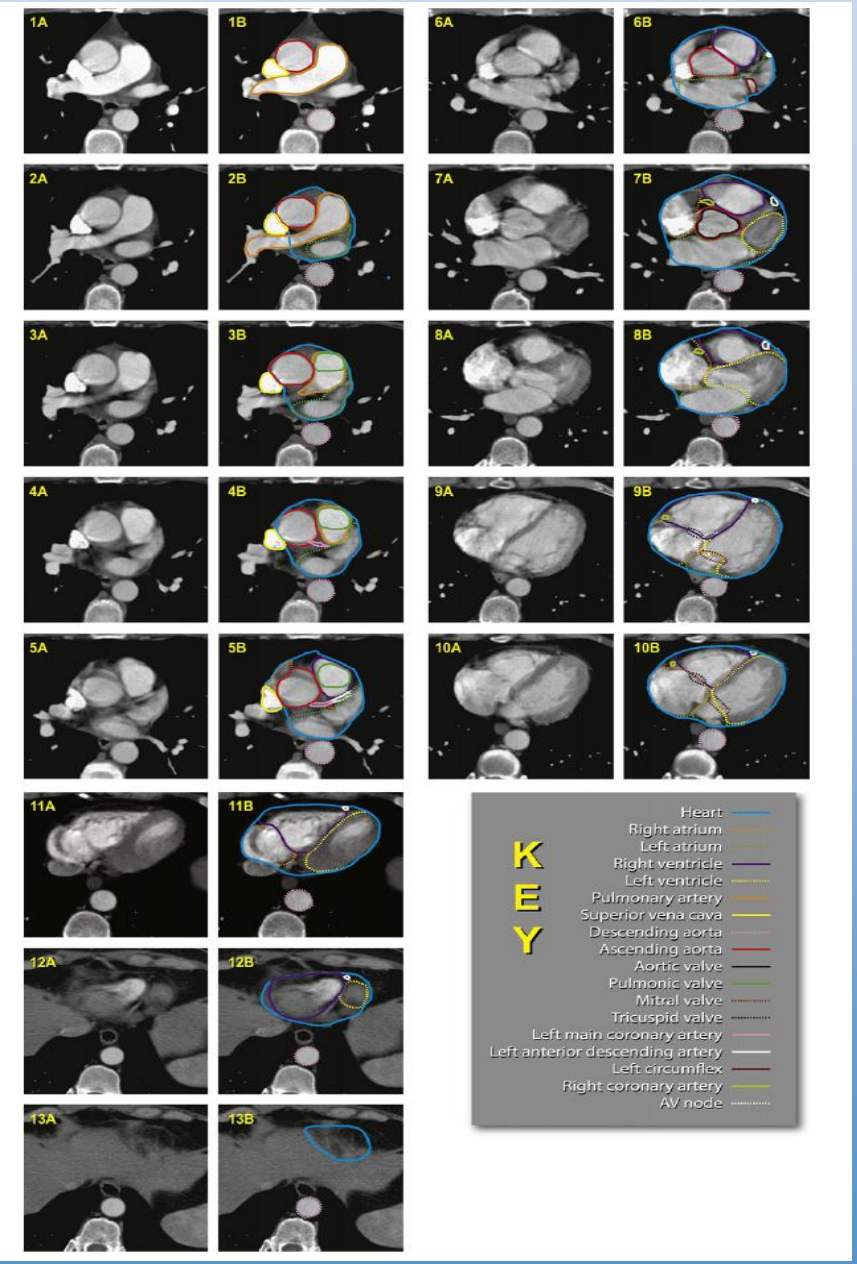
CLINICAL INVESTIGATION **Breast**

DEVELOPMENT AND VALIDATION OF A HEART ATLAS TO STUDY CARDIAC EXPOSURE TO RADIATION FOLLOWING TREATMENT FOR BREAST CANCER

« Despite the known associations of radiation with longterm cardiac effects, no consistent dose-volume correlations have been found. This is likely due to the lack of detailed dosimetric studies with consistent cardiac substructure volume delineation. In this study, we created and validated an atlas which may be used in future efforts to determine such correlations and which can ultimately serve to set standard dosimetric limits to the heart »

Feng *et al*. Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 10–18, 2011



Est-ce que les nouvelles techniques de radiothérapie pourront répondre à la diminution du risque cardio/cérébro-vasculaire

Lymphome de Hodgkin ?

Cancer du sein ?

Cancer tête-et-cou ?

CLINICAL INVESTIGATION **Breast**

CARDIAC EXPOSURES IN BREAST CANCER RADIOTHERAPY: 1950s–1990s

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IJROBP 2007

whole heart doses of **0.9–14 Gy for left-sided**
0.4–6 Gy for right-sided.

Internal mammary chain RT delivered heart doses of 3–17 Gy (left) and 2–10 Gy (right)

the dose to the left anterior descending coronary artery was greater than the heart dose.

CLINICAL INVESTIGATION **Breast**

CARDIAC DOSE FROM TANGENTIAL BREAST CANCER RADIOTHERAPY IN THE YEAR 2006

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IJROBP 2008

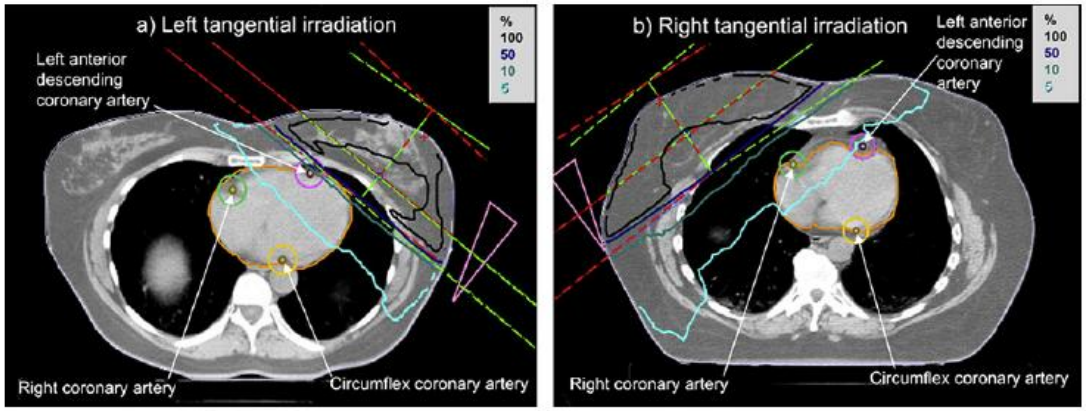


Fig. 1. Dose distribution from 6 MV tangential irradiation. The heart is outlined in orange. The coronary arteries are outlined, and a radial margin of 1 cm has been added to each.

Calcul des HDV, sur 50 patientes traitées par RT (cancer du sein gauche) en 2006 (UK)

Dose moyenne au cœur 2,3 Gy
Dose artère coronaire descendante 7,6 Gy
44 % de patients ont un volume de cœur qui reçoit une dose > à 20 Gy

Pour le cancer du sein, l'amélioration de la balistique devrait limiter le risque

IRSN

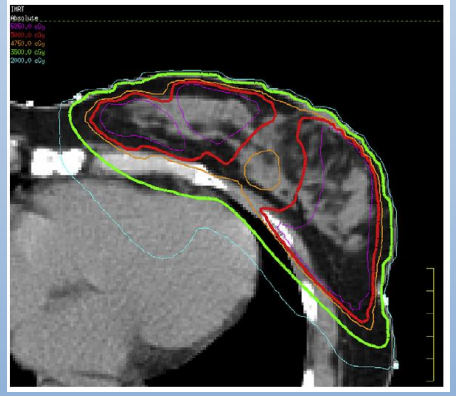
CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 1, pp. 104–110, 2010 **Breast**

TOMOTHERAPY AND MULTIFIELD INTENSITY-MODULATED RADIOTHERAPY PLANNING REDUCE CARDIAC DOSES IN LEFT-SIDED BREAST CANCER PATIENTS WITH UNFAVORABLE CARDIAC ANATOMY

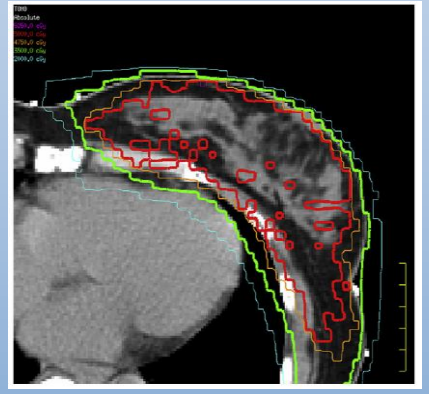
ALAN B. COON, M.D., PH.D.,* ADAM DICKLER, M.D.,† MICHAEL C. KIRK, PH.D.,‡ YIXIANG LIAO, PH.D.,* ANAND P. SHAH, M.D.,* JONATHAN B. STRAUSS, M.D.,* SEA CHEN, M.D., PH.D.,* JULIUS TURIAN, PH.D.,* AND KATHERINE L. GRIEM, M.D.*

3D-CRT

IMRT



Helicoidal Tomotherapy



Coeur

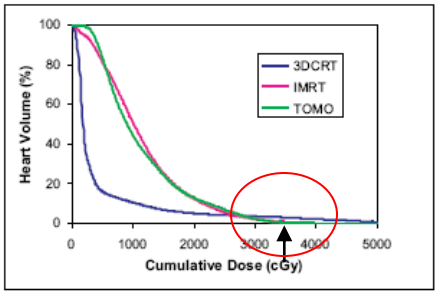


Fig. 7. Mean dose–volume histograms for the heart. 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; TOMO = helical tomotherapy.

Ventricule gauche

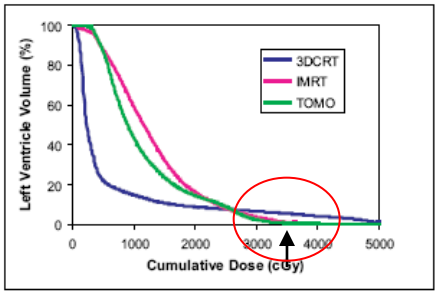
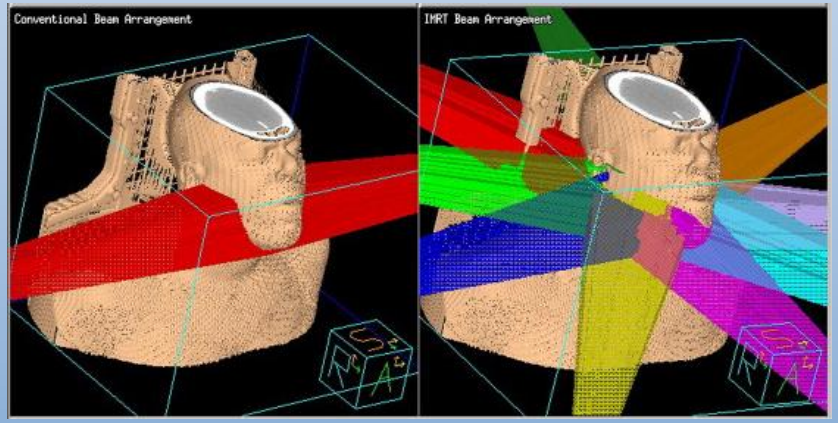


Fig. 8. Mean dose–volume histograms for the left ventricle. 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; TOMO = helical tomotherapy.

Cancer tête-et-cou et nouvelles techniques de radiothérapie

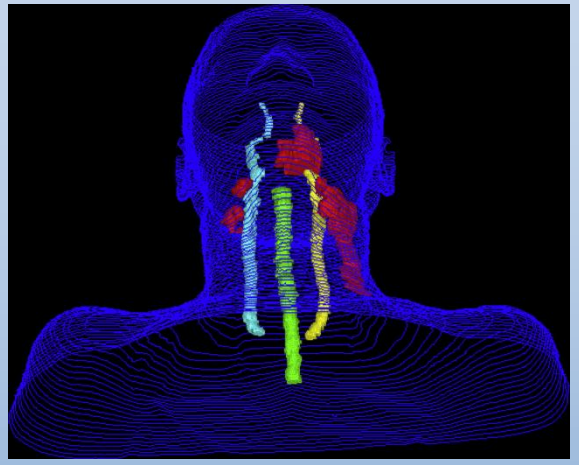
Radiothérapie conformationnelle-3D (3D-CRT)



Radiothérapie conformationnelle avec modulation d'intensité (IMRT)

Cancer tête-et-cou et nouvelles techniques de radiothérapie: le risque cérébrovasculaire toujours d'actualité

rouge
volume tumoral macroscopique
bleu jaune
carotides



Vitolo *et al.*,
Radiother Oncol, 2009

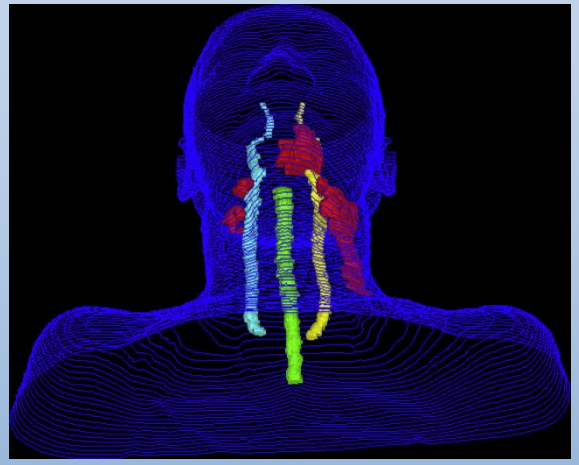
16 patients (USA)
2003-2006
IMRT 70 Gy

Doses reçues aux glandes salivaires

	Mean dose	
Salivary glands	3D-CRT (SD)	IMRT (SD)
Parotid ipsilateral	44.4 (16.7)Gy	28.7 (11.9)Gy
Parotid contralateral	41.6 (14.5)Gy	23.3 (11.2)Gy
Parotid both	43.0 (15.4)Gy	27.1 (12.0)Gy

Doses reçues aux carotides ?

rouge
volume tumoral macroscopique
bleu jaune
carotides



	IMRT	3D-CRT
	All	All
Dmean (Gy)	65.7 60.7–71.0	58.4 52.7–68.0
Dmax (Gy)	77.5 71.6–85.5	75 64.0–82.7

Effets des rayonnements ionisants et pathologies cardiovasculaires :

Aspects physiopathologiques et mécanismes moléculaires

Formation d'une plaque d'athérosclérose

Pathologie inflammatoire de la paroi artérielle qui résulte d'une agression initiale de l'endothélium vasculaire principalement par les lipoprotéines athérogénes »

Plusieurs phases successives d'évolution

✓ Activation /dysfonction endothélial (par les ox-LDL)

✓ Adhesion et infiltration de monocytes et macrophages

✓ Absorption de LDL oxydées (Ox-LDL) par les macrophages sous-endothéliaux : formation de cellules spumeuses accumulation et formation de stries lipidiques

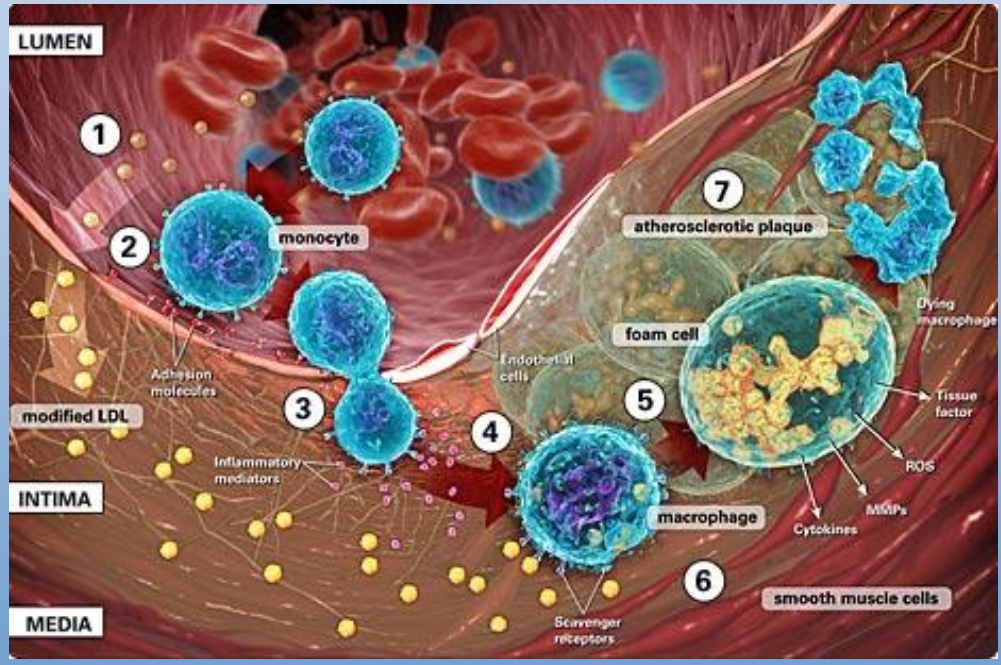
✓ mort des cellules spumeuses (apoptose/ nécrose) provoque 1 dépôt de cholestérol puis formation d'un corps lipidique (type IV).

✓ Inflammation avec libération de cytokines et/ou des facteurs de croissance générée par les Ox-LDL par l'activation des macrophages, endothélium et CML.

✓ Migration et prolifération des CML de la média vers l'intima, formation d'une chape fibreuse.

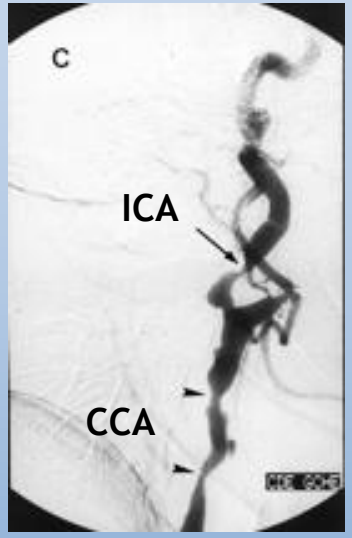
✓ Rupture possible de la plaque thrombus, occlusion.

✓ accident vasculaire ischémique aigu (angor instable, infarctus du myocarde, accident vasculaire cérébral).

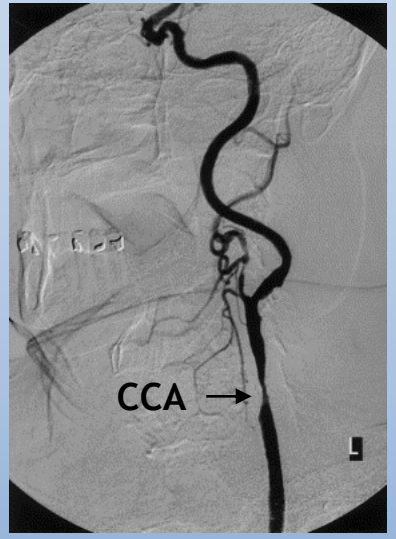


L’athérome radioinduit a-t-il la même étiologie que l’athérome « classique »?

Données cliniques: sténoses carotidiennes radioinduites



Houdart *et al.*, Stroke, 2001



Modrall and Sadjadi,
Semin Vasc Surg, 2003

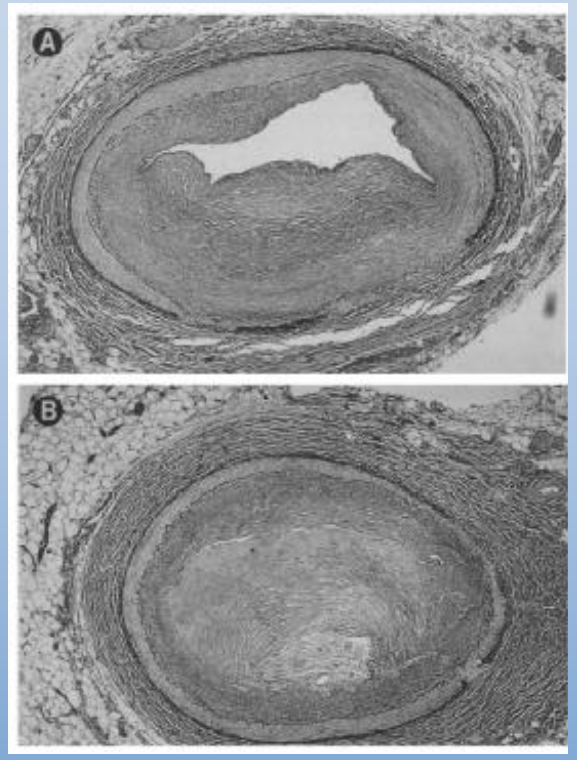
Similarité:

- Aspect des clichés d'angiographie

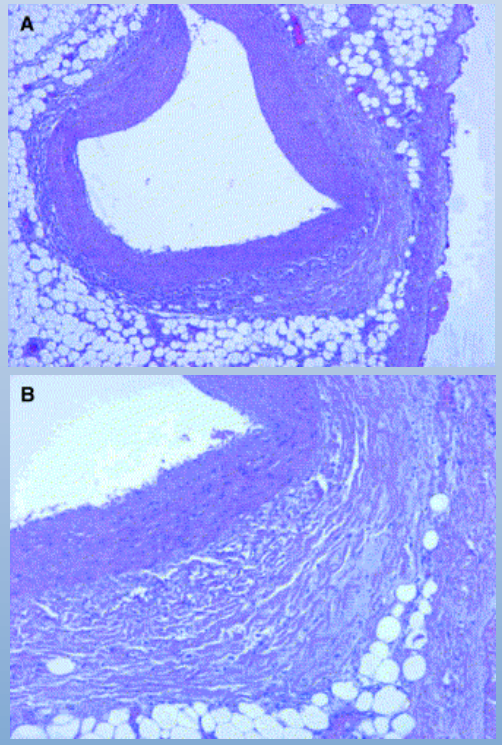
Différences:

- Lésions sur des patients plus jeunes
- Site de localisation atypique des lésions (CCA)
- Lésions confinées au site irradié (pas associées à des occlusions coronariennes et périphériques)
- Pathologies occlusives dans l'artère carotide interne (pas d'atteinte du bulbe carotidien)
- Longueur de la sténose plus importante
- Fibrose périartérielle et des tissus sains (traitement chirurgical plus difficile)

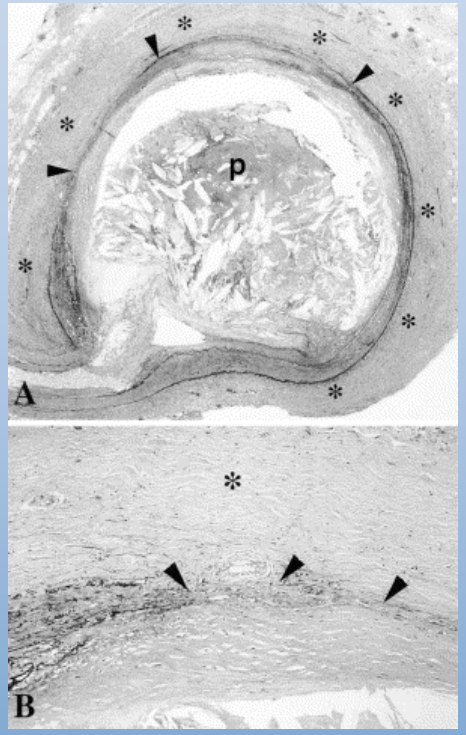
Données histologiques: artères coronaires (lymphome Hodgkin)



Veinot and Edwards, Hum Pathol, 1996



Miltenyi *et al.*, Cardiovasc Radiat Med, 2004



Virmani *et al.*, Cardiovasc Radiat Med, 1999

Similarité:

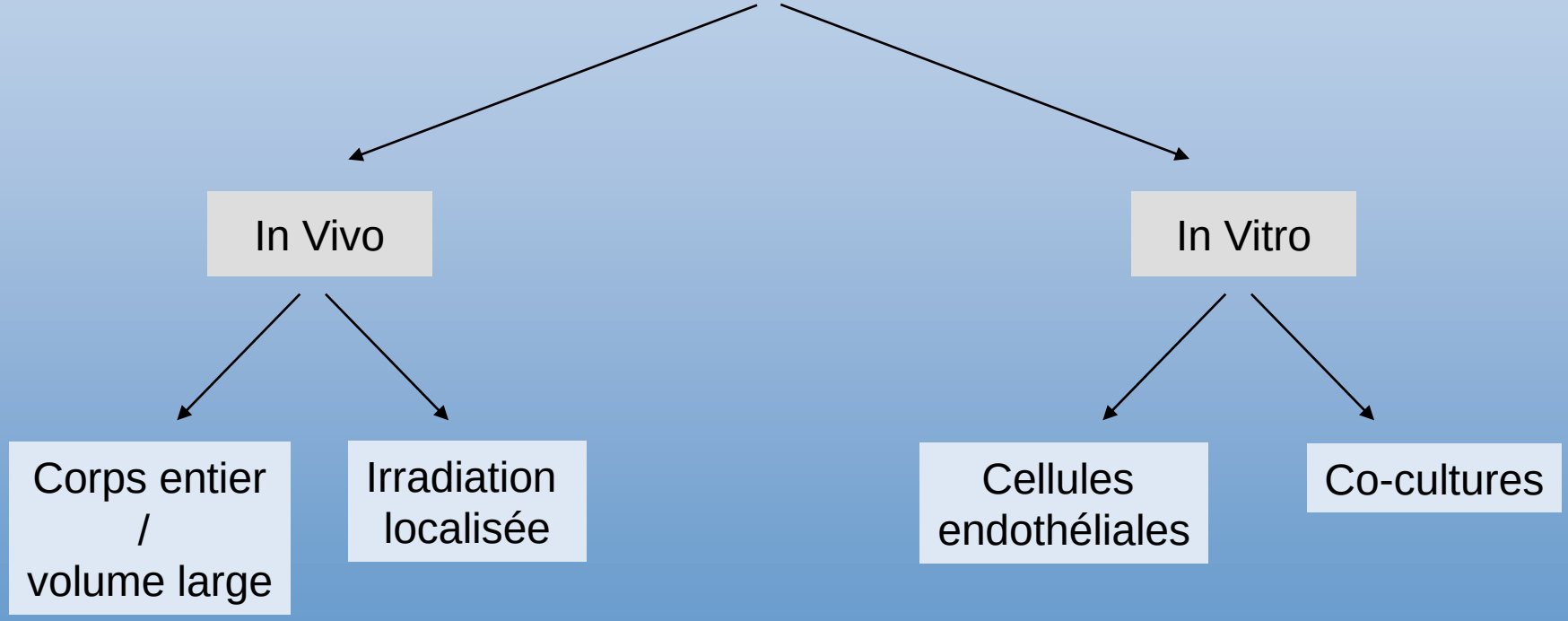
- Aspect de la plaque? (lipides, fibrose)

Différences:

- Fibrose sévère et étendue de l'intima
- Amincissement voire destruction focalisée de la média
- Fibrose et épaississement de l'adventice
- Sténose ostiale (plutôt que distale)

Données Expérimentales

Modéles expérimentaux pour
l'étude des complications « cardio-vasculaires » ou « vasculaires » radio-induites



Problèmes et limites

L'endothélium vasculaire

Barrière
Contrôle perméabilité vasculaire

Anti-thrombogène
Anti-coagulante
Pro-fibrinotylique

Inflammation

Croissance vasculaire

Tonus vasculaire

In vitro

Orientation de l'endothélium vers un phénotype, pro-coagulant, pro-thrombotique, pro-inflammatoire et anti-fibrinolytique

Concept d'activation chronique de l'endothélium vasculaire

In vitro

Orientation de l'endothélium vers un phénotype, pro-coagulant, pro-thrmobotique, proinflammatoie et antifibrynolytique

Concept d'activation chronique de l'endothélium vasculaire

Pertinence en clinique de ces observations ?

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Radiation Injury

Sustained Inflammation Due to Nuclear Factor-Kappa B Activation in Irradiated Human Arteries

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Caroline Gahm, MD, PHD,§ Hanna E. Agardh, BA,† Filip Farnebo, MD, PHD,*
Per Tornvall, MD, PHD†‡

Table 1 Demographic and Clinical Characteristics

Age (yrs)/Sex	RT Dose (Gy)	Time After RT (weeks)	Tissue Transfer	Current Smoking	CVD
60/M	64	500	Forearm	No	Hypertension
77/F	54	4.5	Fibula	Yes	
46/M	64	5	Forearm	Yes	
68/F	64	45	Forearm	No	
60/M	50	6.5	Forearm	No	
48/M	64	150	Fibula	No	
59/M	68	30	Fibula	No	Past CVL
67/M	N/A	N/A	Fibula	No	Hypertension
47/F	N/A	N/A	Forearm	No	
50/F	54	4	Forearm	Yes	
49/F	64	20	Forearm	No	Hypertension
59/M	54	7	Forearm	Yes	
50/M	64	91	Forearm	No	

CVD = cardiovascular disease; CVL = cerebrovascular lesion; RT = radiotherapy.

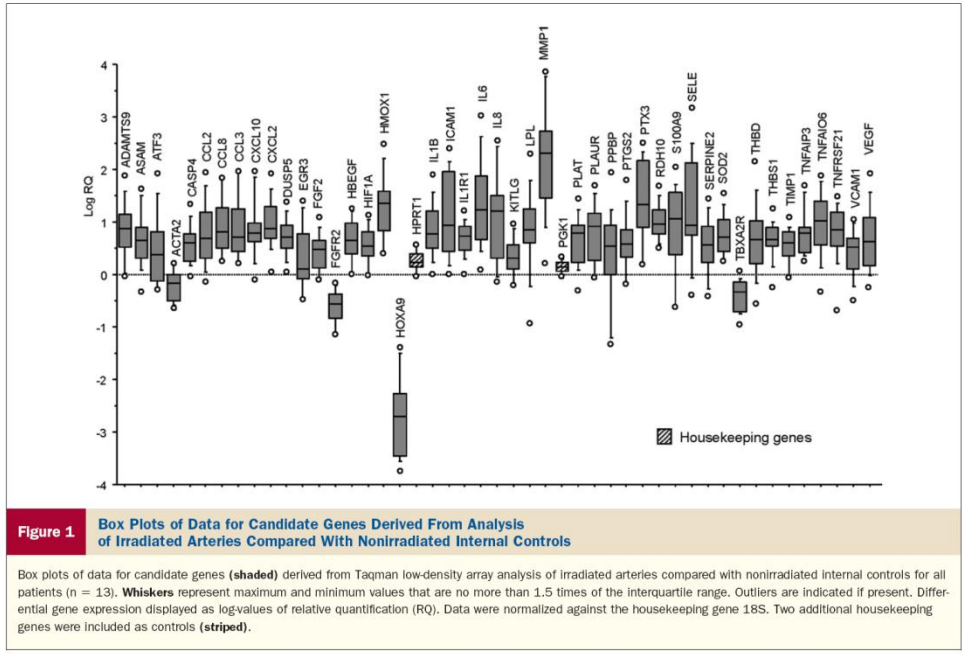


Figure 1 Box Plots of Data for Candidate Genes Derived From Analysis of Irradiated Arteries Compared With Nonirradiated Internal Controls

Box plots of data for candidate genes **(shaded)** derived from Taqman low-density array analysis of irradiated arteries compared with nonirradiated internal controls for all patients (n = 13). **Whiskers** represent maximum and minimum values that are no more than 1.5 times of the interquartile range. Outliers are indicated if present. Differential gene expression displayed as log-values of relative quantification (RQ). Data were normalized against the housekeeping gene 18S. Two additional housekeeping genes were included as controls **(striped)**.

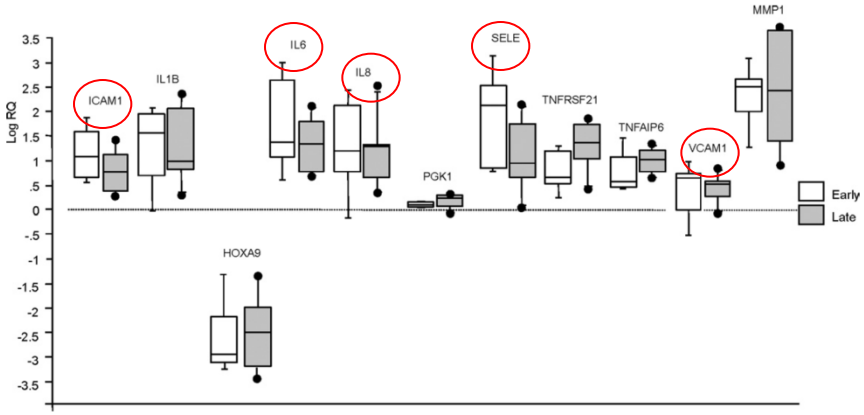


Figure 2 **Box Plot of NF-κB Related Genes Derived From Analysis of Irradiated Arteries Compared With Controls**

Box plot of nuclear factor-κ B (NF-κB)-related genes derived from Taqman low-density array analysis of irradiated arteries compared with controls for patients where time elapsed from termination of radiotherapy to operation was registered (n = 11). **Whiskers** represent maximum and minimum values that are no more than 1.5 times of the interquartile range. Outliers are indicated if present. Data were normalized against the housekeeping gene 18S. Selected genes with particular interest for inflammation are shown together with the housekeeping gene PGK1. Patients are divided into 2 groups according to the accepted nomenclature of early **(open)** and late **(shaded)** effects of radiotherapy, with time ranging from 4 to 7 weeks and 20 to 500 weeks, respectively. Differential gene expression displayed as log-values of relative quantification (RQ).

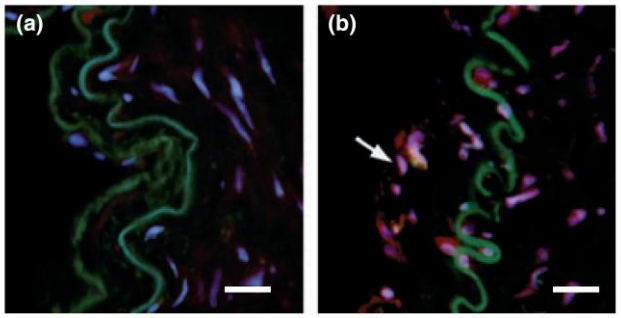


Fig. 3 *Immunofluorescence staining of an irradiated cervical artery showing co-localization of p65 and cell nuclei (in purple; indicating the presence of activated NF-κB) (b) compared to a healthy nonirradiated radial artery, from the same patient, showing only staining for cell nuclei (in blue) (a). Scale bar = 20 μm.*

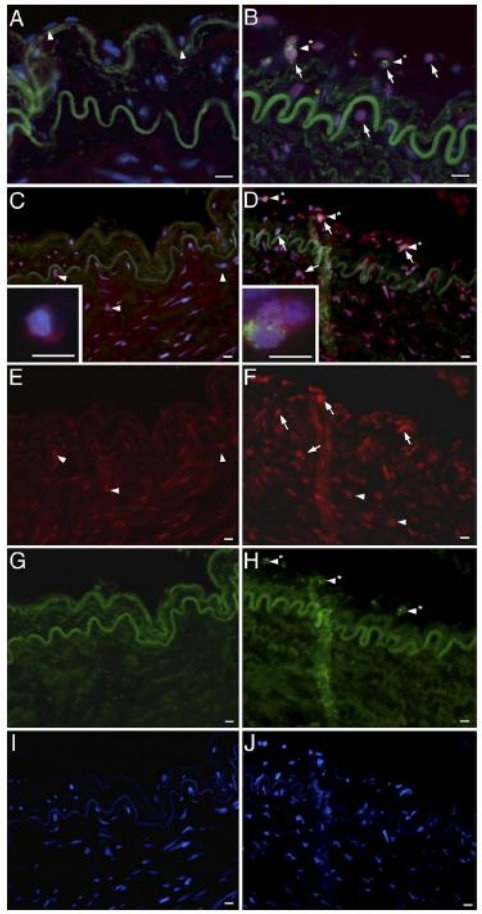
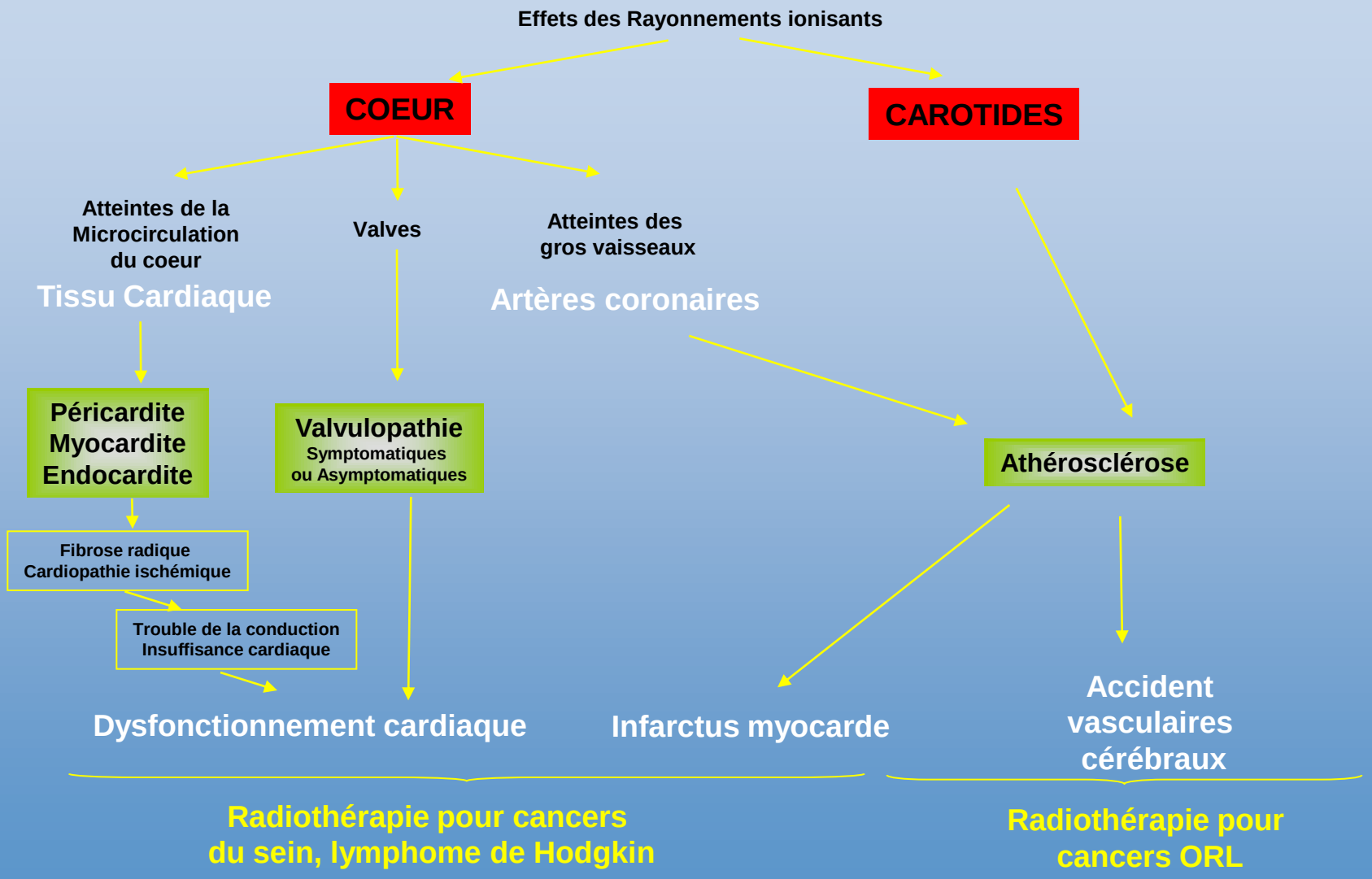


Figure 5 **Staining of p65 Subunit Superimposed on Photographs of DAPI Nuclear Staining**

Staining of p65 subunit (red fluorescence) superimposed on photographs of 4',6-diamidino-2-phenylindole (DAPI) nuclear staining (blue fluorescence) indicating nuclear factor-κB (NF-κB)-activation by nuclear translocation seen with co-localization of p65 and DAPI in the cell nucleus (purple) in irradiated arteries (B, D) compared with non-irradiated arteries (A, C). Co-staining for CD68 (green) showed that the p65 subunit was localized to the nuclei in macrophages but only present in radiated arteries. Single channel stainings of the merged photographs (C and D) are visualized for nonirradiated (E, G, I) and irradiated (F, H, J) arteries from the same patient, irradiated 4 years before harvest of biopsies, representative for stainings of nonirradiated and irradiated arteries in 3 patients (arrows = p65 nuclear stains; arrowhead = p65 expression in the cytoplasm; arrowhead asterisk = p65 nuclear staining positive cells co-expressed with CD68 in the cytoplasm). Bar = 10 μm.

In vivo : comment modéliser ?



10 Gy total body irradiation increases risk of coronary sclerosis, degeneration of heart structure and function in a rat model

Baker *et al.* *Int. J. Radiat. Biol.*, Vol. 85, No. 12, December 2009, pp. 1089–1100

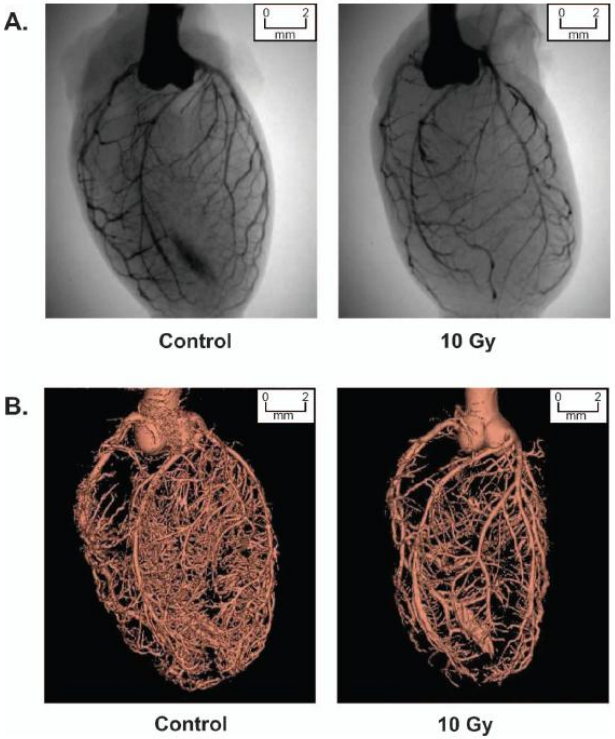


Figure 3. Coronary vessel changes. (A) Micro-computerised tomography images of isolated rat heart with contrast agent perfused through the coronary arteries. Representative image of a heart obtained 120 days after exposure to 10 Gy compared with an age matched control. The limit for visualisation of coronary vessel diameter is 4 μm. (B) Three-dimensional micro-computed tomography reconstruction of coronary network showing density of coronary vessels at 120 days following 10 Gy TBI compared with an age-matched control. TBI resulted in a decrease in the density of the smaller diameter coronary vessels (<50 μm). The density of large diameter coronary vessels was unchanged following 10 Gy TBI.

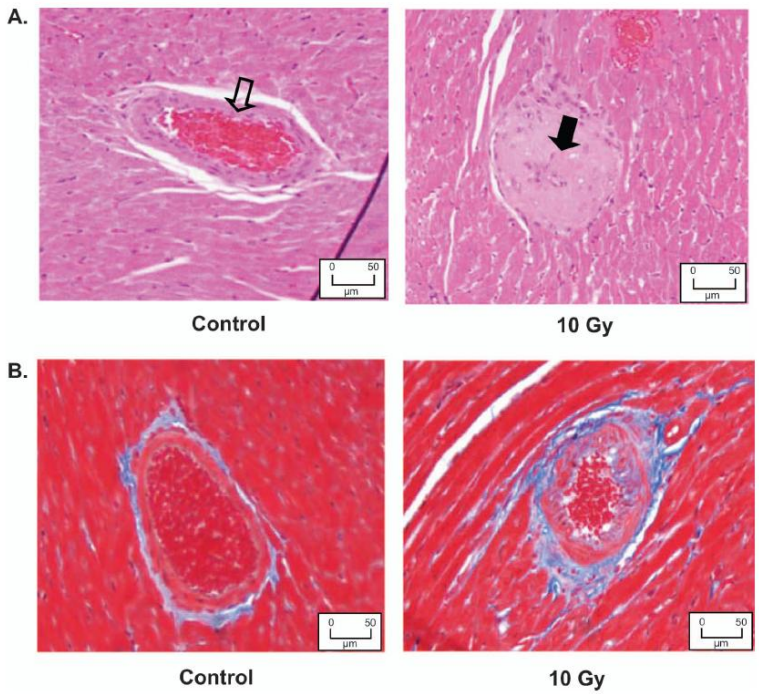


Figure 4. Morphological changes. (A) Heart sections stained with H&E show vessel lumen completely blocked (➡) as a result of myointimal proliferation 120 days after 10 Gy TBI. Three hearts were studied in each group. The lumen of a comparable vessel in an age matched heart is patent and contains red blood cells (⇨). (B) Heart section stained with Trichrome showing increased peri-arterial fibrosis in small caliber coronary vessel 120 days after 10 Gy TBI compared with a comparable vessel in an age matched control. Three hearts were studied in each group. Fibrosis appears as blue using trichrome staining.

→ **Modèle d'atteintes microvasculaires à l'origine cardiopathies ischémiques, fibrotiques**

Modéles précliniques les plus pertinents ?

BIOLOGY CONTRIBUTION Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 2, pp. 552–559, 2007

THE IMPACT OF HEART IRRADIATION ON DOSE–VOLUME EFFECTS IN THE RAT LUNG

Peter van Luijk, Ph.D.,* Hette Faber,*† Harm Meertens, Ph.D.,* Jacobus M. Schippers, Ph.D.,‡ Johannes A. Langendijk, Ph.D., M.D.,* Sytze Brandenburg, Ph.D.,§ Harm H. Kampinga, Ph.D.,† and Robert P. Coppes, Ph.D.*†

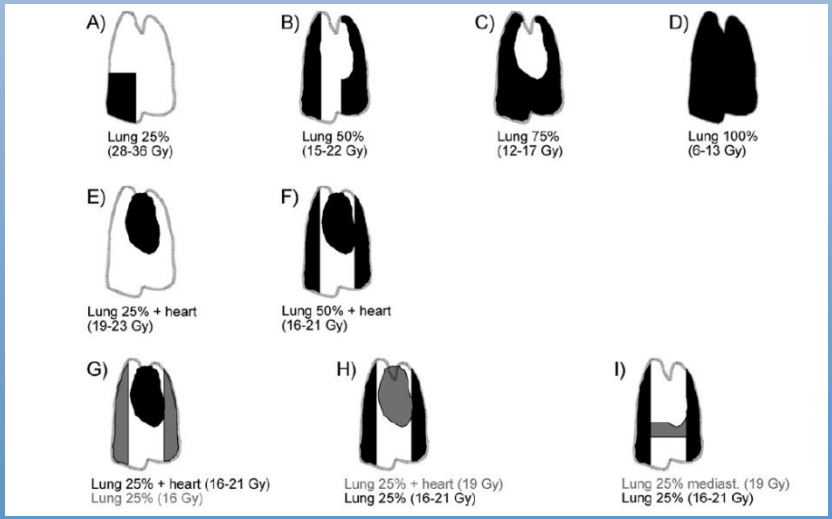
American Journal of Pathology, Vol. 168, No. 2, February 2006

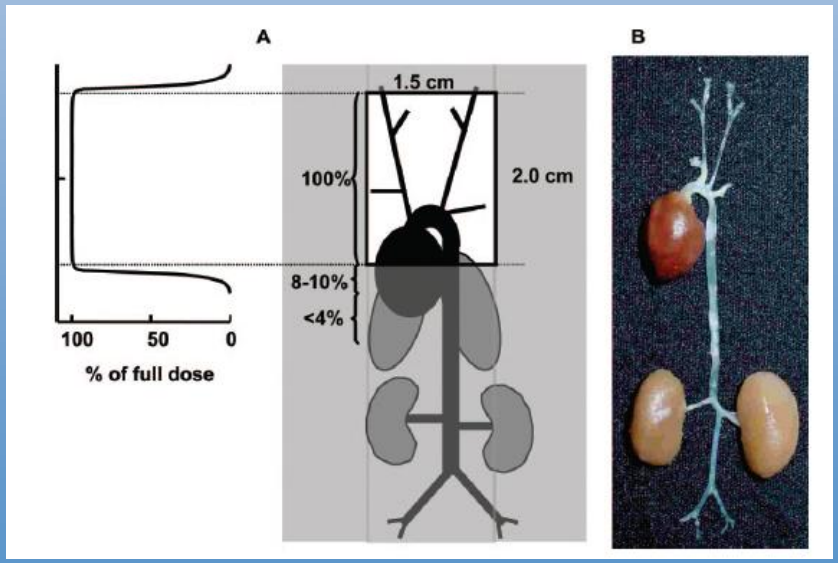
DOI: 10.2353/ajpath.2006.050409

Vascular Biology, Atherosclerosis and Endothelium Biology

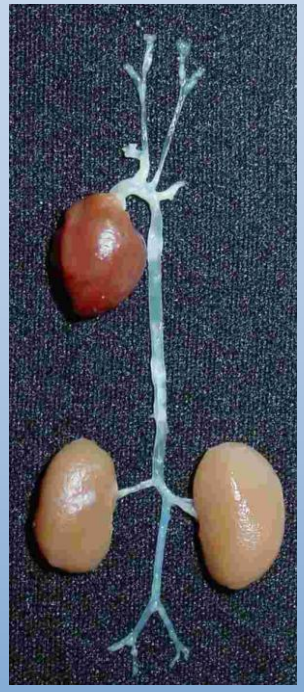
Ionizing Radiation Accelerates the Development of Atherosclerotic Lesions in ApoE$^{-/-}$ Mice and Predisposes to an Inflammatory Plaque Phenotype Prone to Hemorrhage

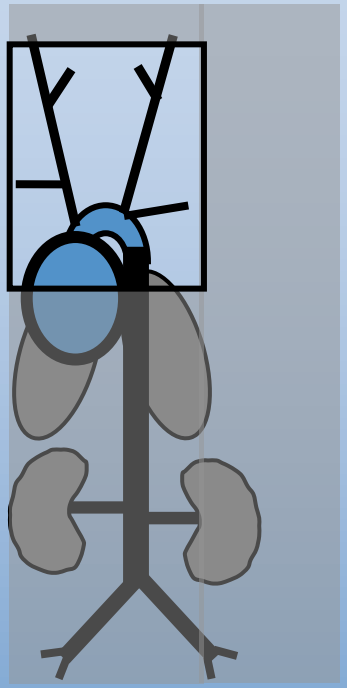
Stewart *et al*

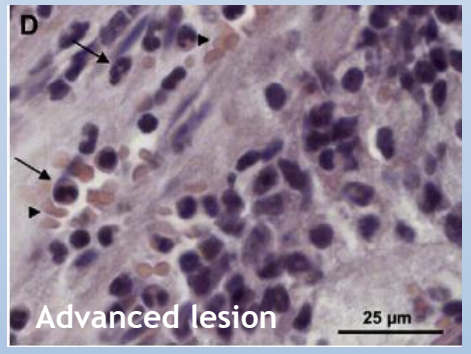


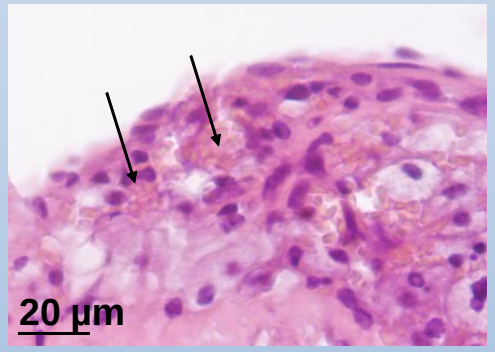


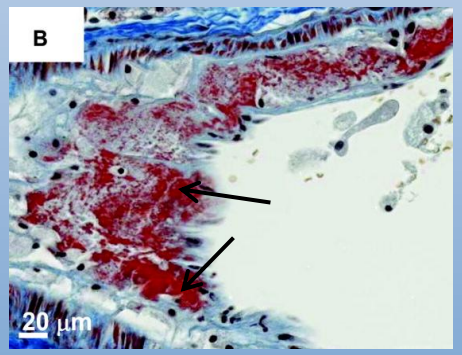
Données expérimentales: nombre et taille des plaques

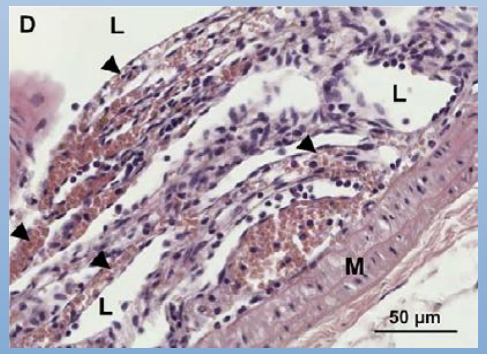












Souris C57BL/6J ApoE$^{-/-}$

Irradiation:

- 8 ou 14 Gy dose unique
- 20x2 Gy (5 fractions/sem)

Analyse artères carotides :

1, 4, 22, 28, 30, 34 sem

Plaques avancées des souris ApoE$^{-/-}$ irradiées

- plus de granuleux
- macrophages contenant des érythrocytes
- dépot de fibrine augmenté
- hémorrhagie intraplaque
- diminution de la quantité de collagène
- inflammatoire et instable

Saske Hoving, NCI Amsterdam
Unpublished and Int J Radiat Oncol Biol Phys 2008
Stewart *et al.*, Am J Pathol, 2006

Modélisation expérimentale des lésions vasculaires radio-induites chroniques aux fortes doses est complexe

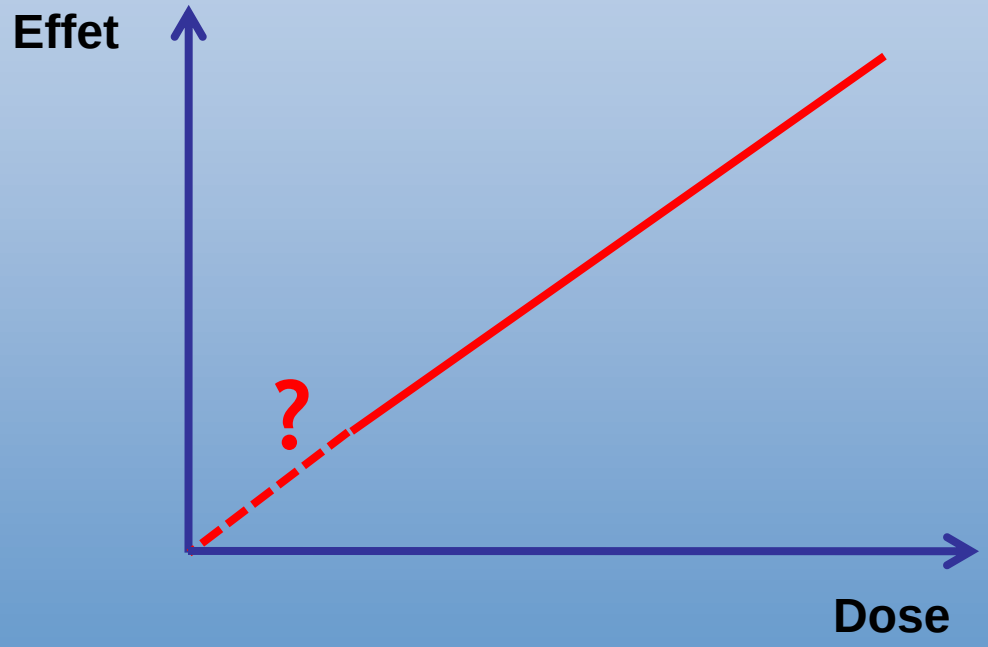
Mécanismes moléculaires et cellulaires sont encore mal connus

Athérosclérose radio-induite et / ou Accélération de l'athérosclérose par les RI ?

Quelles sont les spécificités de l'athérosclérose RI ?

Effets des rayonnements et pathologies cardiovasculaires :

cas des faibles doses ?



BMJ

RESEARCH

Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003

Shimizu et al. 2010

Objective : To investigate the degree to which ionising radiation confers risk of mortality from heart disease and stroke.
Participants 86 611 Life Span Study cohort members with individually estimated radiation doses from 0 to >3 Gy (86% received <0.2 Gy).
Main outcome measures Mortality from stroke or heart disease as the underlying cause of death and dose response relations with atomic bomb radiation.

Table 2 | Summary excess relative risks (ERR)* per Gy and excess additive risks per 10^4 person year Gy† (EAR/10^4 PY-Gy) for types of circulatory disease mortality

Circulatory disease	Indicated as underlying cause of death				Underlying or contributing cause of death	
	Deaths	P value	% ERR/Gy (95% CI)	EAR/10^4 PY-Gy (95% CI)†	Deaths	% ERR/Gy (95% CI)
Total	19 054	<0.001	11 (5 to 17)	5.5 (2.7 to 8.4)	25 113	15 (10 to 20)
Stroke	9 622	0.02	9 (1 to 17)	2.3 (0.4 to 4.4)	12 139	12 (5 to 19)
Heart disease	8 463	<0.001	14 (6 to 23)	3.2 (1.3 to 5.2)	14 018	18 (11 to 25)
Other	969	>0.5	2 (−18 to 29)	0.1 (−0.4 to 0.7)	5 846	58 (45 to 72)

*Estimates based on linear model, adjusted for city, sex, age at exposure, and attained age.
†Average EARs calculated directly from fitted ERR models.

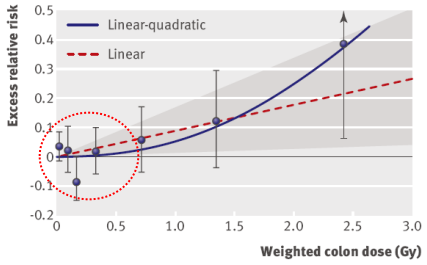


Fig 1 | Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

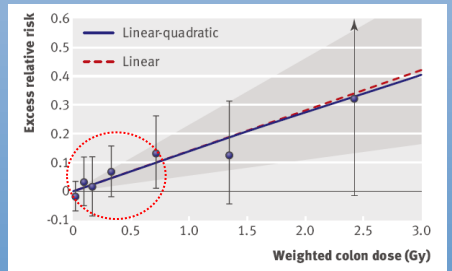


Fig 2 | Radiation dose-response relation (excess relative risk) for death from heart disease, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

« Doses > 0.5 Gy are associated with an elevated risk of both stroke and heart disease, the degree of risk at lower doses is unclear »

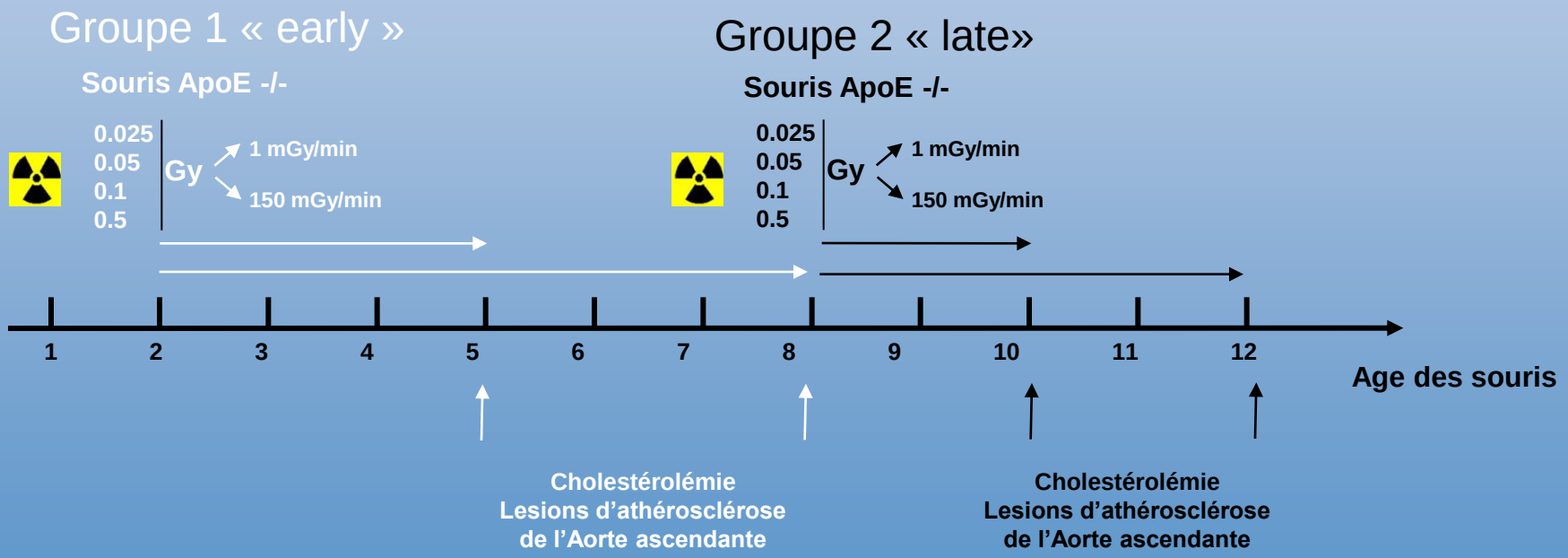
Au niveau expérimental ?

RADIATION RESEARCH
0033-7587/11 $15.00

DOI: 10.1667/RR2176.1

Low-Dose Radiation Exposure and Atherosclerosis in *ApoE*$^{-/-}$ Mice

R. E. J. Mitchel,[a,1] M. Hasu,[b,c] M. Bugden,[a] H. Wyatt,[a] M. P. Little,[d] A. Gola,[e] G. Hildebrandt,[f] N. D. Priest[a] and S. C. Whitman[b,c,2]



Dose unique sauf les 0.5 Gy à 1 mGy/min délivré en 5 fraction de 100 mGy 5 jours consécutifs

TABLE 1
Summary of Measured Responses to Low-Dose Exposure

	LDR Early stage	HDR Early stage	LDR Late stage	HDR Late stage
Lesion frequency	↓	↓	↑	—
Lesion size	↓	↓	↓	—
Lesion severity	—	↑	↓	↓
Serum cholesterol	—	↑	↓	—
% Lesion lipid in macrophages	—	↓ ↑	N.D.	N.D.

Notes. LDR, low-dose-rate exposure. HDR, high-dose-rate exposure. Downward arrows indicate a decrease and upward arrows an increase in the measured parameter. A horizontal line indicates no change, and N.D. indicates that the end point was not measured. The arrows indicate that the response was observed at some dose and time after exposure but do not indicate that there may have also been a lack of response at some other dose or time.

✓Résultats sont non-linéaires avec la dose
✓ Effets maximum sont observés pour les doses de 25 et 50 mGy
✓ Globalement les faibles débit de doses (« early et late ») sont protecteurs et ralentissent la pathologie
✓ Les forts débits de doses sont protecteurs ou délétères selon les groupes « early » et « late »
✓ Certains effets persistent des mois et d'autres sont transitoires

→ Suggèrent que l'extrapolation linéaire du risque observé aux fortes de doses n'est pas appropriée pour les très faibles doses

Conclusion/Discussion

Fortes doses : Radiothérapie :

Le risque existe et l'amélioration de la balistique de résoudra pas tous les problèmes (ex carotides)

Déterminer les patients avec un fort risque (enfant, jeunes adultes, prédisposés)

Besoins d'approche multidisciplinaire : radiothérapeutes/cardiologues, suivi des patients à risque.

Affiner la relation dose /effet : Approches prospectives en épidémiologie avec données dosimétriques précises

Développer le concept d'organe à risque vers structure à risque

Faibles doses :

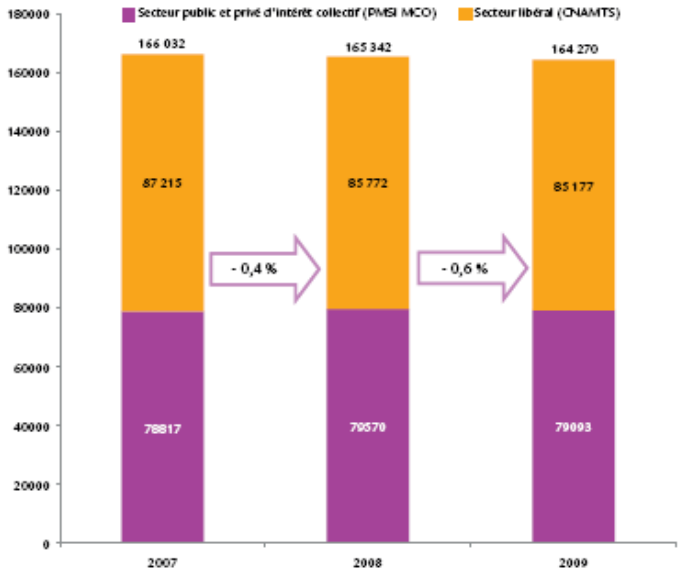
Risque cardiovasculaire et faibles doses : nouvelles cohortes, suivi épidémiologique/moléculaire

Recherche sur les faibles doses : Effets stochastiques ou déterministes

Radioprotection médicale : imagerie cardiaque, diagnostic …, nouvelles populations à risque ?

Merci de votre attention

FIGURE 17 : ÉVOLUTION DU NOMBRE DE PATIENTS TRAITÉS PAR RADIOTHÉRAPIE ENTRE 2007 ET 2009



Source : bases CNAMTS 2007-2009 et PMSI 2007- 2009 – Traitement INCa 2010

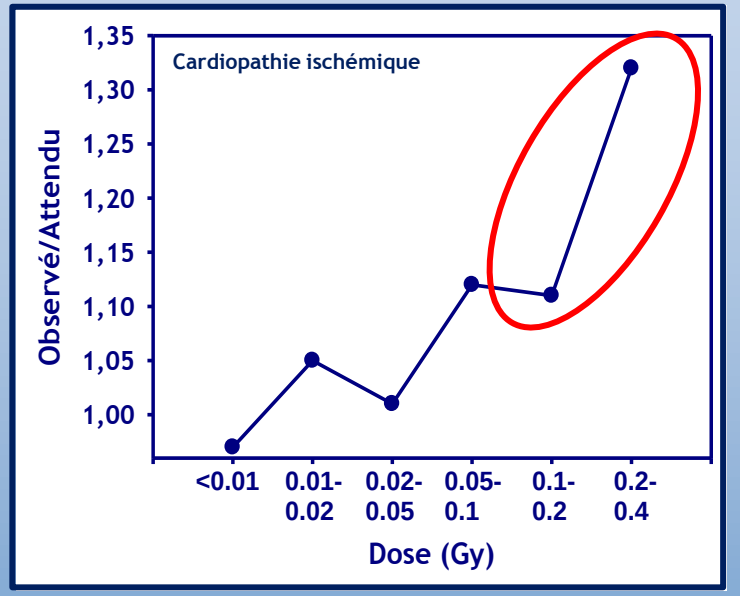
Plus de 1,75 million de séances de radiothérapie en 2009 parmi lesquelles plus de 99 % de traitements en ambulatoire.

Un nombre de séances qui augmente de près de 8 % sur les trois dernières années.

IRSN

Et pour des doses très faibles ? < 0.5 Gy

64937 travailleurs industries nucléaires (UK)
1946-2002, suivi jusqu'en 2005
15 ans d'exposition
Suivi dosimétrique personnalisé (films dosimétriques)
Pathologies cardio et cérébrovasculaires: 8%



Adapté de McGeoghegan *et al.*, Int J Epidemiol, 2008

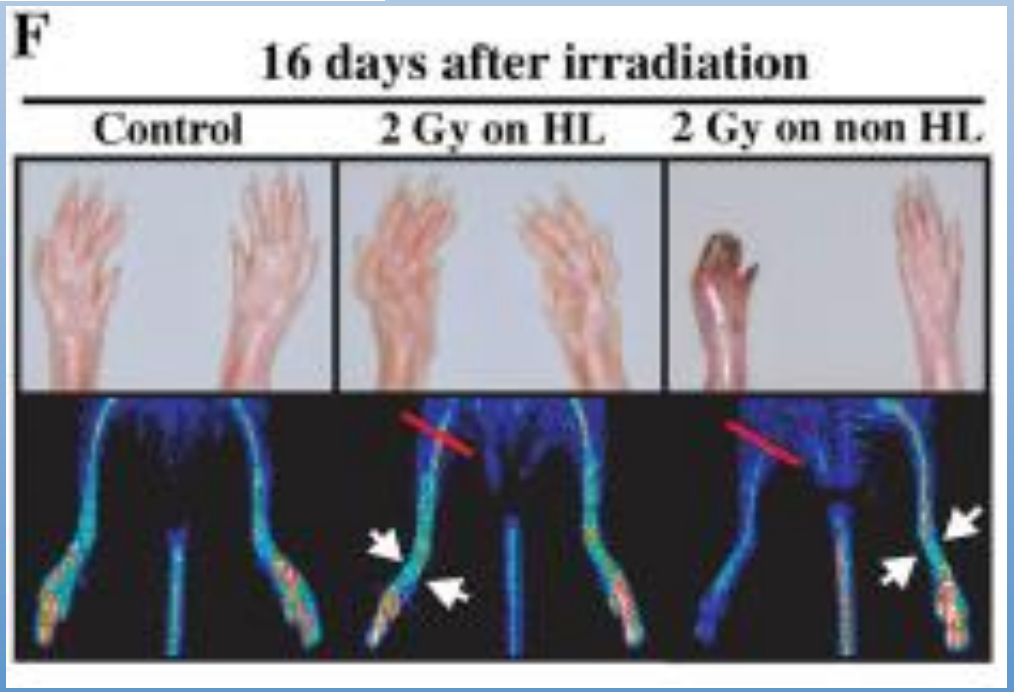
Atteintes vasculaires : Effets bénéfiques !!

Low-dose irradiation promotes tissue revascularization through VEGF release from mast cells and MMP-9–mediated progenitor cell mobilization

Beate Heissig,[1,2] Shahin Rafii,[3] Haruyo Akiyama,[1] Yuichi Ohki,[1] Yayoi Sato,[1] Tejada Rafael,[3] Zhenping Zhu,[4] Daniel J. Hicklin,[4] Ko Okumura,[2] Hideoki Ogawa,[2] Zena Werb,[5] and Koichi Hattori[1,2]

Journal of Experimental Medecine 2005

Modèle ischémie
de la patte chez la souris :



2 gy irradiation localisée :augmentation de la régénération vasculaire en stimulant l'angiogénèse

Effets bénéfiques !!

RADIATION RESEARCH 174, 467–479 (2010)
0033-7587/10 $15.00

DOI: 10.1667/RR1980.1

Acceleration of Diabetic Wound Healing by Low-Dose Radiation is Associated with Peripheral Mobilization of Bone Marrow Stem Cells

Wei-Ying Guo,[a,b] Guan-Jun Wang,[b,1] Ping Wang,[c] Qiang Chen,[d] Yi Tan[e] and Lu Cai[b,e,1]

Rats diabétiques (STZ): modèle de cicatrisation cutanée, des doses de 75 mGy corps entier répétées pendant 5 à 15 jours,

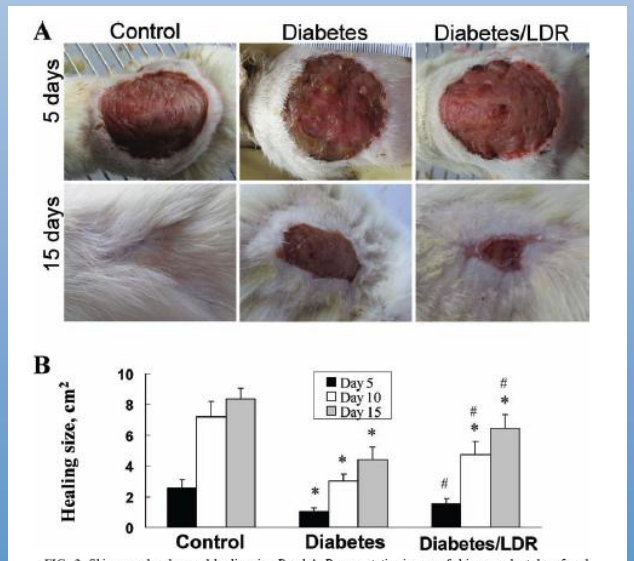


FIG. 2. Skin wound and wound healing size. Panel A: Representative images of skin wounds at days 5 and 15 after wound formation. Healing size was calculated as the difference between the original wound size (9 cm²) and the size of the unhealed area. Data are presented as means ± SD ($n = 8$). LDR: low-dose radiation. *$P <$ 0.05 compared to control; #$P < 0.05$ compared to diabetes.

Accélération de la cicatrisation cutanée via la mobilisation des cellules de la moelle

RADIATION RESEARCH 175, 307–321 (2011)
0033-7587/11 $15.00

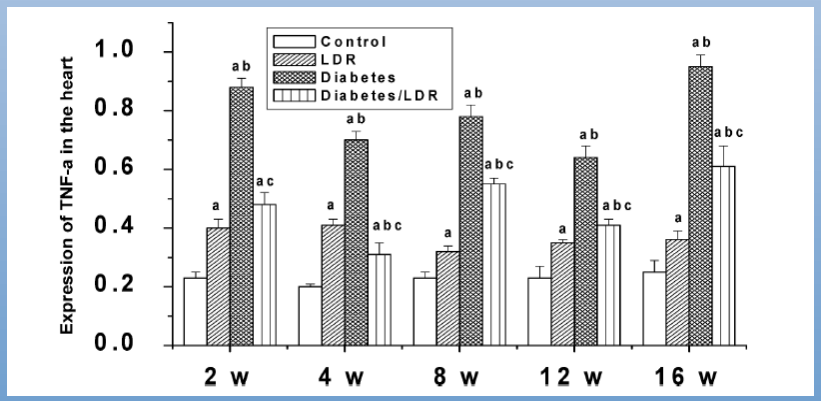
DOI: 10.1667/RR1950.1

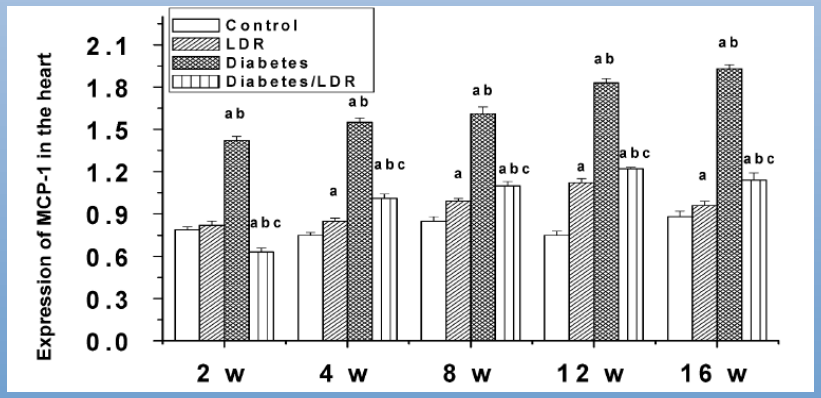
Attenuation of Diabetes-Induced Cardiac Inflammation and Pathological Remodeling by Low-Dose Radiation

Chi Zhang,[a,b,c] Shunzi Jin,[c,1] Weiying Guo,[d] Cai Li,[a,e] Xiaokun Li,[a,c,f] Madhavi J. Rane,[a,g] Guanjun Wang[d] and Lu Cai[a,b,d,1]

Souris STZ exposées à de très faibles doses (25 mGy corps entier, tous les 2 jours pendant 2 à 16 semaines)

Suivi expression dans le cœur de : TNFα, ICAM-1, PAI-1, MCP-1





STZ → TNFα, ICAM-1, PAI-1, MCP-1 ☢ TNFα, ICAM-1, PAI-1, MCP-1

Atténuation de l'inflammation cardiaque induite par la STZ

BRAIN
A JOURNAL OF NEUROLOGY
May 2011

Relationship between the brain radiation dose for the treatment of childhood cancer and the risk of long-term cerebrovascular mortality

Nadia Haddy,[1,2,3] Abdeddahir Mousannif,[1,2,3] Markhaba Tukenova,[1,2,3] Catherine Guibout,[1,2,3] Jacques Grill,[2] Frédéric Dhermain,[2] Hélène Pacquement,[4] Odile Oberlin,[2] Chiraz El-Fayech,[1,2,3] Carole Rubino,[1,2,3] Cécile Thomas-Teinturier,[1,2,3] Marie-Cécile Le-Deley,[1,2,3] Mike Hawkins,[5] Dave Winter,[5] Jean Chavaudra,[2] Ibrahima Diallo[1,2,3] and Florent de Vathaire[1,2,3]

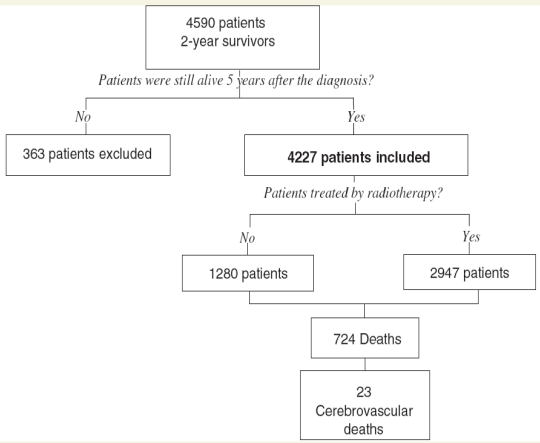


Figure 1 Selection of the population of interest. The flow chart describes the selection process for this study.

Temps de suivi médian : 30 ans

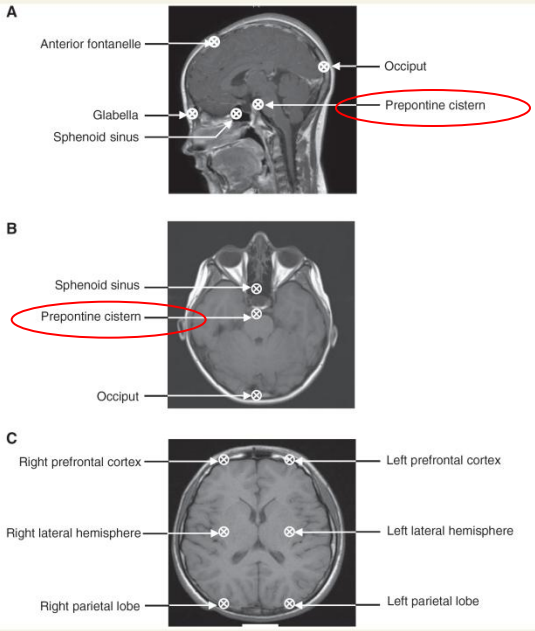


Figure 2 Location of dose estimation points in the brain illustrated on CT images. (**A**) This image shows the position of five dose estimation points (anterior fontanelle, glabella, sphenoid sinus, occiput and prepontine cistern) in the median sagittal plane. (**B**) Shows the sphenoid sinus, prepontine cistern and occiput points in the transverse plane, at the level of the orbits. (**C**) Shows the position of the six other dose estimation points (right and left prefrontal, right and left hemisphere and right and left parietal) in the transverse plane at the ventricular level.

Table 3 Relative risks of death from cerebrovascular diseases in a French–UK cohort of 4127 5-year childhood cancer survivors

Treatment exposure	Cerebrovascular disease mortality				
	Number of patients	Number of deaths	Absolute risk per year (95% CI)/1000	Relative risk[a] (95% CI)	*P*-value
Alkylating agents					
No	2282	17	0.29 (0.7–0.45)	1 (ref)	
Yes	1945	6	0.16 (0.06–0.31)	1.5 (0.3–6.9)	>0.5
Vinca alkaloids					
No	1873	17	0.34 (0.21–0.53)	1 (ref)	
Yes	2354	6	0.13 (0.05–0.26)	0.4 (0.1–2.1)	0.3
Anthracyclines					
No	2996	21	0.28 (0.8–0.42)	1 (ref)	
Yes	1231	2	0.09 (0.01–0.27)	0.5 (0.07–3.4)	0.5
Antimetabolites					
No	3640	20	0.23 (0.14–0.35)	1 (ref)	
Yes	587	3	0.26 (0.66–0.68)	1.9 (0.4–8.8)	0.4
Radiation dose to the prepontine cistern (Gy)					
No radiotherapy	1936	4	0.03 (0.02–0.15)	1 (ref)	
<10	1133	4	0.16 (0.07–0.31)	1.5 (0.4–6.1)	0.6
10 < 30	373	3	0.36 (0.09–0.93)	3.7 (0.8–16.9)	0.1
30 < 50	363	6	0.90 (0.36 –1.81)	11.4 (3.0–42.3)	0.01
50+	167	5	1.61 (0.58–3.46)	17.8 (4.4–73.0)	<0.0001
Not available	255	1	0.17 (0.10–0.75)	1.7 (0.2–15.6)	0.6

Ref = reference group.
a Cox model adjusted for all the other treatment variables in the table, gender, follow-up interval after diagnosis, age at diagnosis and treatment period.

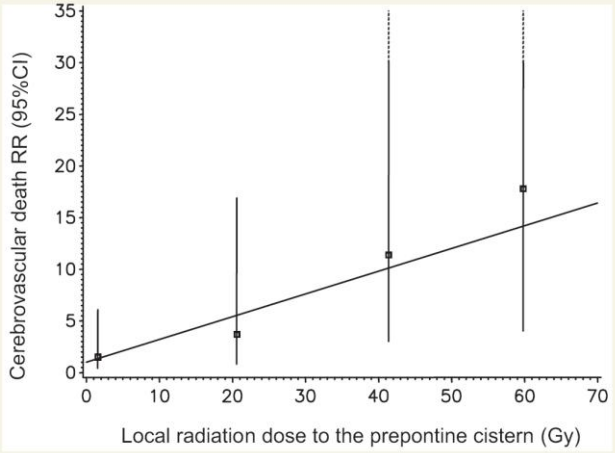


Figure 4 Relative risk (RR) of death due to cerebrovascular disease according to the radiation dose to the prepontine cistern. The curve represents the RR of death from a cerebrovascular disease as a linear function of the radiation dose to the prepontine cistern: RR = 1 + 0.22 * dose. Vertical bars represent 95% CI.

En 2009, on peut estimer[19] que les 156 000 traitements réalisés par RTC 3D représentent 80 % de l'ensemble des traitements.

En 2009, la majorité des centres (64 %) réalisaient plus de 75 % de leurs traitements par RTC3D, alors qu'ils n'étaient que 40 % en 2007. Si on constate une progression notable des traitements délivrés par cette technique standard, 8 % des centres donnaient encore insuffisamment accès à la RTC 3D fin 2009 (pour moins de la moitié de leurs traitements).