DIGNE DE CONFIANCE,
à chaque instant

27 septembre 2019
Session 11h-11h30

CENTRE INTÉGRÉ DE SANTÉ ET DE SERVICES SOCIAUX DE LAVAL

Les avancées en cancer pulmonaire en 2019: quoi de neuf en radiothérapie?

Dre Édith Filion, FRCPC
Radio-oncologie

Centre hospitalier de l'Université de Montréal
CHUM

Québec

DIGNE DE CONFIANCE,
à chaque instant

Divulgation conflits d'intérêts

AUCUN

Centre intégré
de santé
et de services sociaux
de Laval
Québec

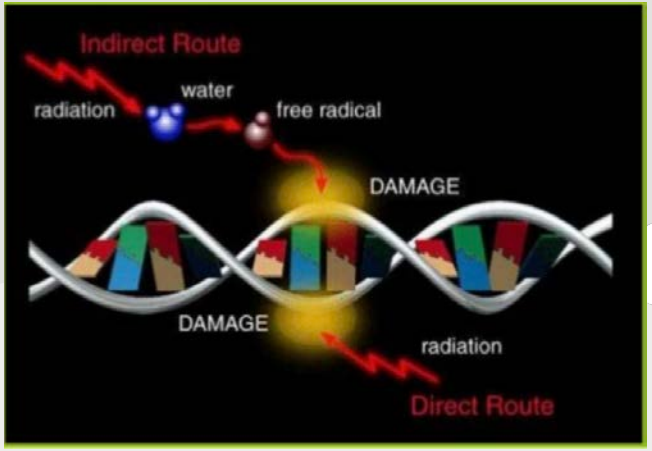
Les avancés en cancer pulmonaire en 2019: quoi de neuf en radiothérapie?

Objectifs

- À la suite de cette présentation, le participant devra être en mesure de :
- Décrire les nouveautés en radiothérapie en intention curative pour le cancer pulmonaire
- Connaître le rôle de la radiothérapie dans la maladie oligométastatique

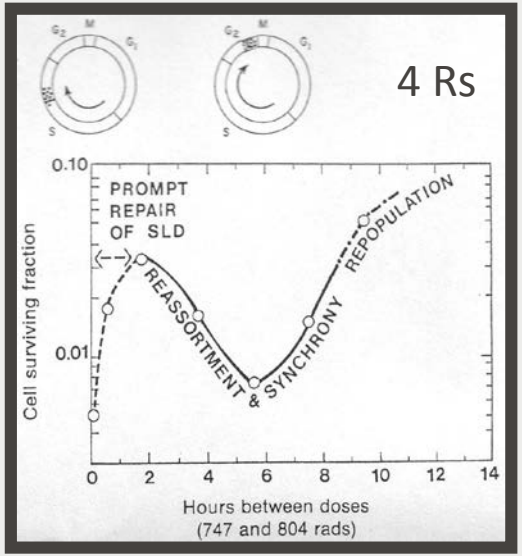
Plan de la présentation

- Introduction à la radiothérapie et technologies actuelles
- Nouveautés en stade précoce et en stade localement avancé
- Nouveautés en stade oligométastatique
- L’avenir technologique en radiothérapie
- Conclusion

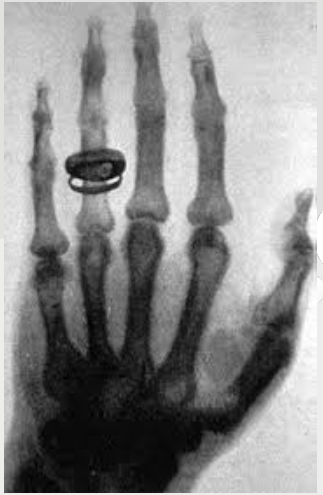


- Radiation ionisante pour traiter tumeurs malignes (occasionnellement bégnines)

- Administrer avec précision la dose au volume tumoral en minimisant le dommage aux tissus sains environnants.



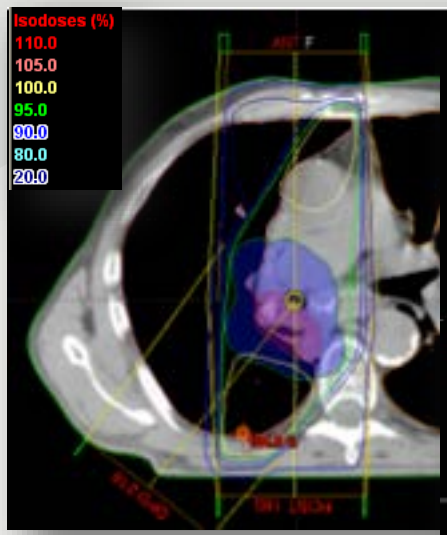
Perspective



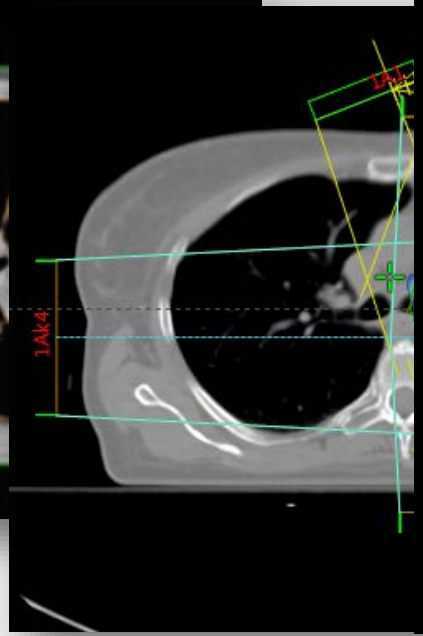
- Utilisation remonte au 19e siècle
  - Rayons X décrit en 1895 par Roentgen
  - Découverte du radium par Marie and Pierre Curie en 1898
- Radiothérapie joue un rôle chez >50% patients avec cancer
- Révolutions technologiques nombreuses
  - Amélioration des techniques d'imagerie
  - Amélioration des techniques d'administration de la radiothérapie
  - Modèles pour prédire comportement du cancer et choix d'approche

DIGNE DE CONFIANCE,
à chaque instant

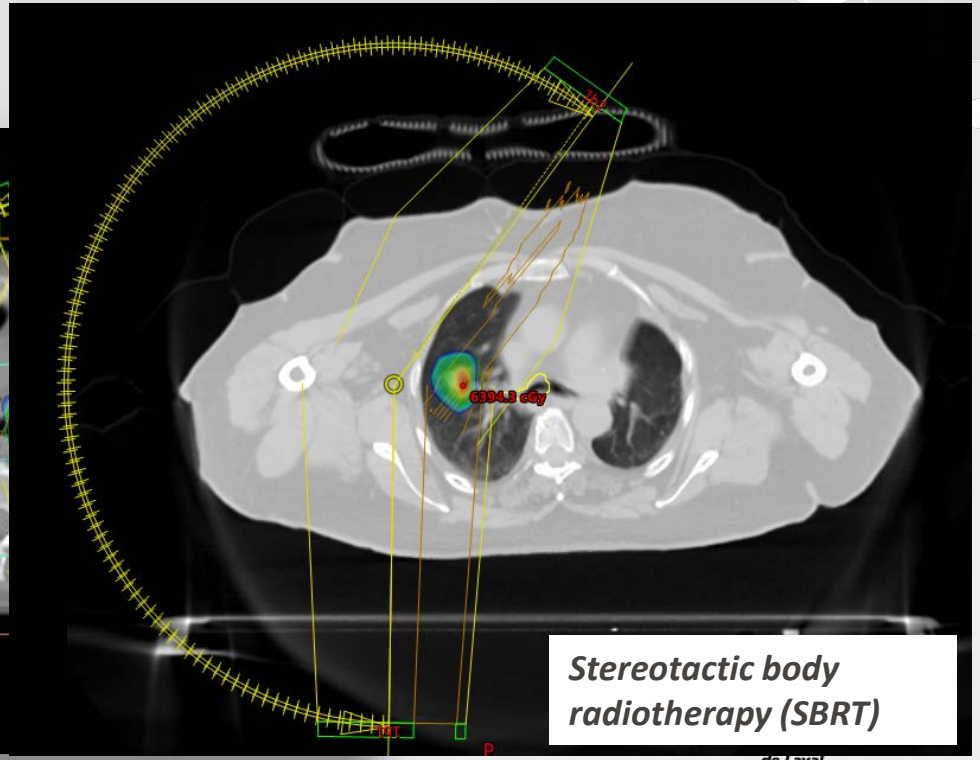
Révolution des techniques de la radiothérapie



3D- Conforme (3DCRT)



Intensity Modulated Radiotherapy (IMRT)



Stereotactic body radiotherapy (SBRT)

de Laval Québec

VOLUME 35 · NUMBER 1 · JANUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

Stephen G. Chun, Chen Hu, Hak Choy, Ritsuko U. Komaki, Robert D. Timmerman, Steven E. Schild, Jeffrey A. Bogart, Michael C. Dobelbower, Walter Bosch, James M. Galvin, Vivek S. Kavadi, Samir Narayan, Puneeth Iyengar, Clifford G. Robinson, Raymond B. Wynn, Adam Raben, Mark E. Augspurger, Robert M. MacRae, Rebecca Paulus, and Jeffrey D. Bradley

Taux de pneumonite radique = 8% 3D-CRT vs 4% IMRT, p= .039

Table 5. Multivariable Logistic Regression Analysis of CTCAE ≥ Grade 3 Pneumonitis

Covariate	Comparison	OR (95% CI)	*P*
RT technique	3D-CRT (RL) *v* IMRT	0.410 (0.171 to 0.986)	.046
AJCC stage group	IIIA (RL) *v* IIIB	2.276 (1.009 to 5.137)	.048
Lung V20, %	Continuous	1.071 (1.008 to 1.137)	.026
PTV, mL	Continuous (log-transformed)	1.701 (0.708 to 4.085)	.235

DIGNE DE CONFIANCE,
à chaque instant

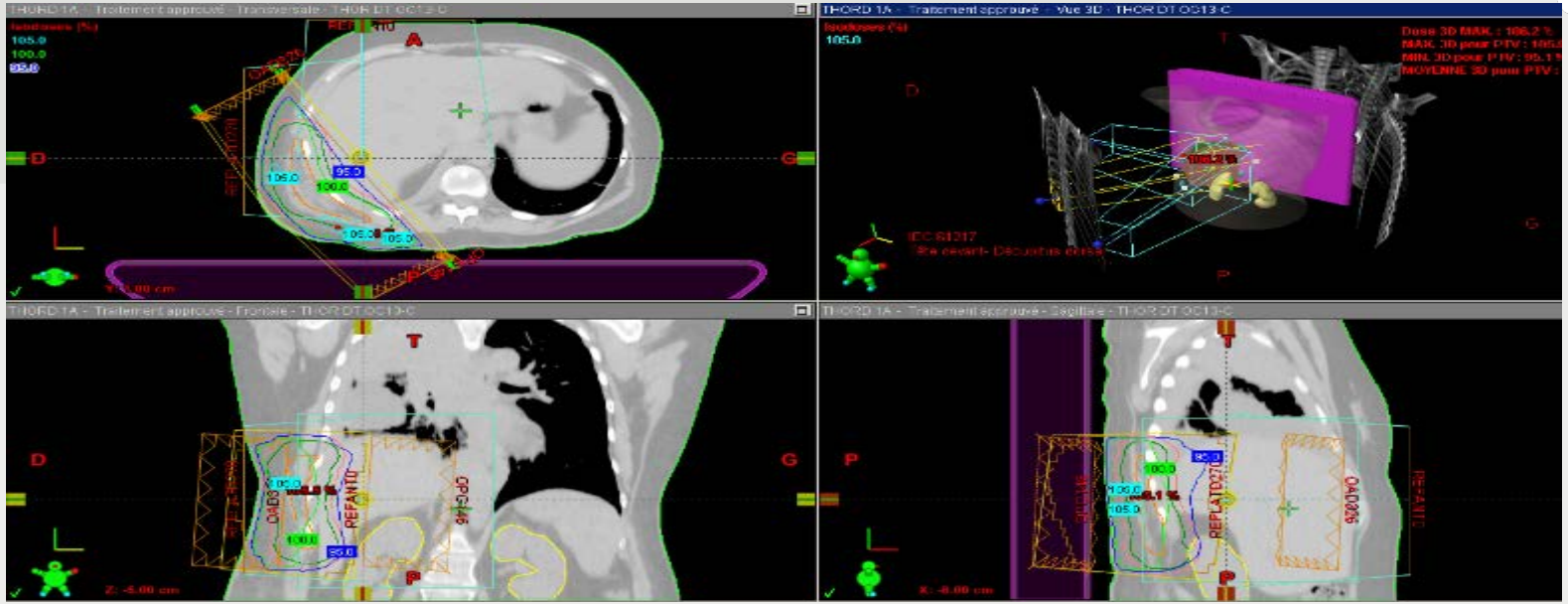
Planifica

1. Positi
2. CT sca … sque d'imm … us)
3. Transf … ion
4. IRM o
5. Délim … ologue
6. Dosim … d'entrée)
7. Appro

Centre intégré de santé et de services sociaux de Laval
Québec

DIGNE DE CONFIANCE,
à chaque instant

La dosimétrie:
Calcul de la dose et de la répartition de la radiation dans le volume irradié



Centre intégré
de santé
et de services sociaux
de Laval

Québec

L’arsenal thérapeutique en radiothérapie

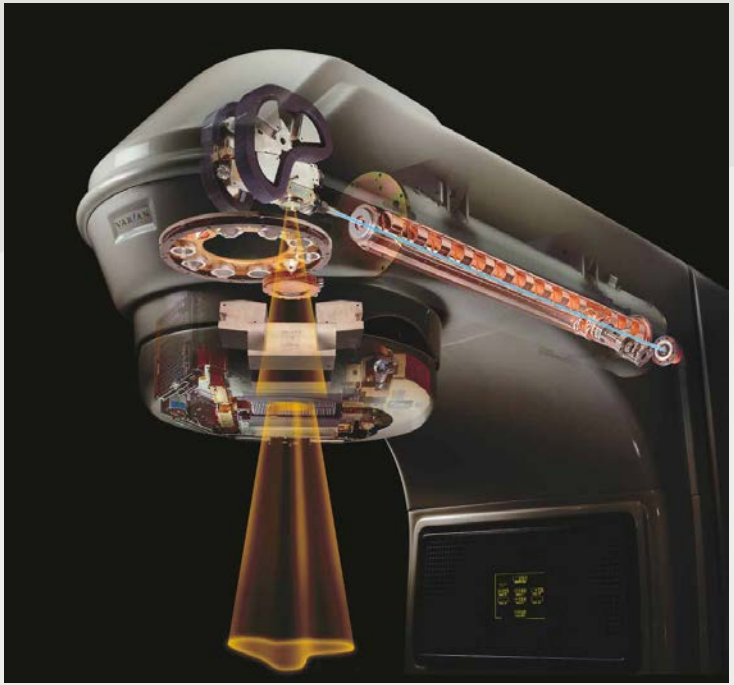
Planification du traitement

- CT 4D / CT 5 D
- MR Linac

Administration du traitement

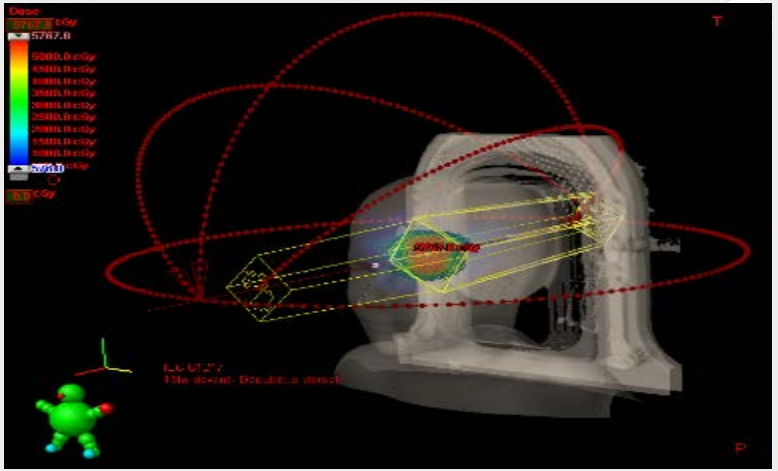
- IMRT / IGRT / SBRT
- Appareils de traitement
- Gestion du mouvement
- Suivi per traitement

Accélérateur linéaire (Linac)



Nouvelle génération de Linac (arcthérapie)

- Radiothérapie délivrée sous forme d’arc
- Diminution du temps de traitement
- Amélioration du gradient de dose



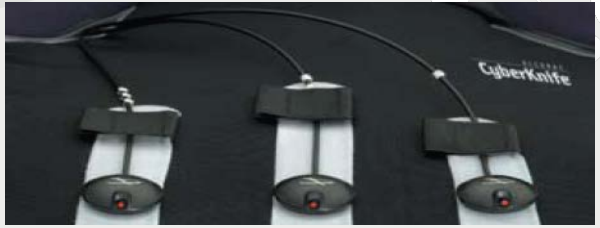
Cyberknike

- Accélérateur linéaire 6 MV
- Robot (précision 0.3-0.7 mm)
- Table motorisée
- Système de planification de traitement
- Système de repérage par rayons-x, détecteurs d'images

CYBERKNIFE À SIX
DEGRÉS DE LIBERTÉ

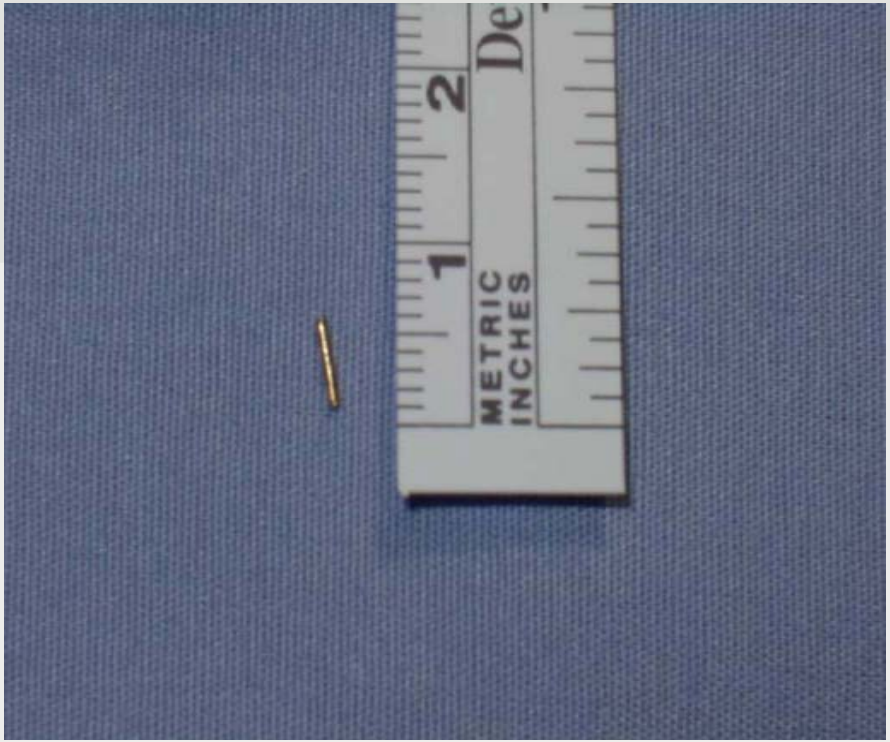
Guidage en temps réel -Synchrony®

- Suivi en temps réel de la tumeur avec la respiration
- Doit obligatoirement être utilisé en combinaison avec une méthode de détection automatique de la tumeur ou de son susbtitut
    - XSight Lung (tumeur)
    - Fiducials (susbtitut)

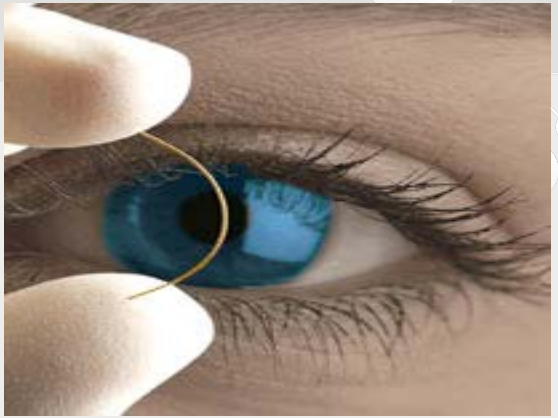


DIGNE DE CONFIANCE,
à chaque instant

Marqueurs fiduciaires



Grains d'or



Visicoil TM

Centre intégré
de santé
et de services sociaux
de Laval

Québec

DIGNE DE CONFIANCE,
à chaque instant

Tomothérapie

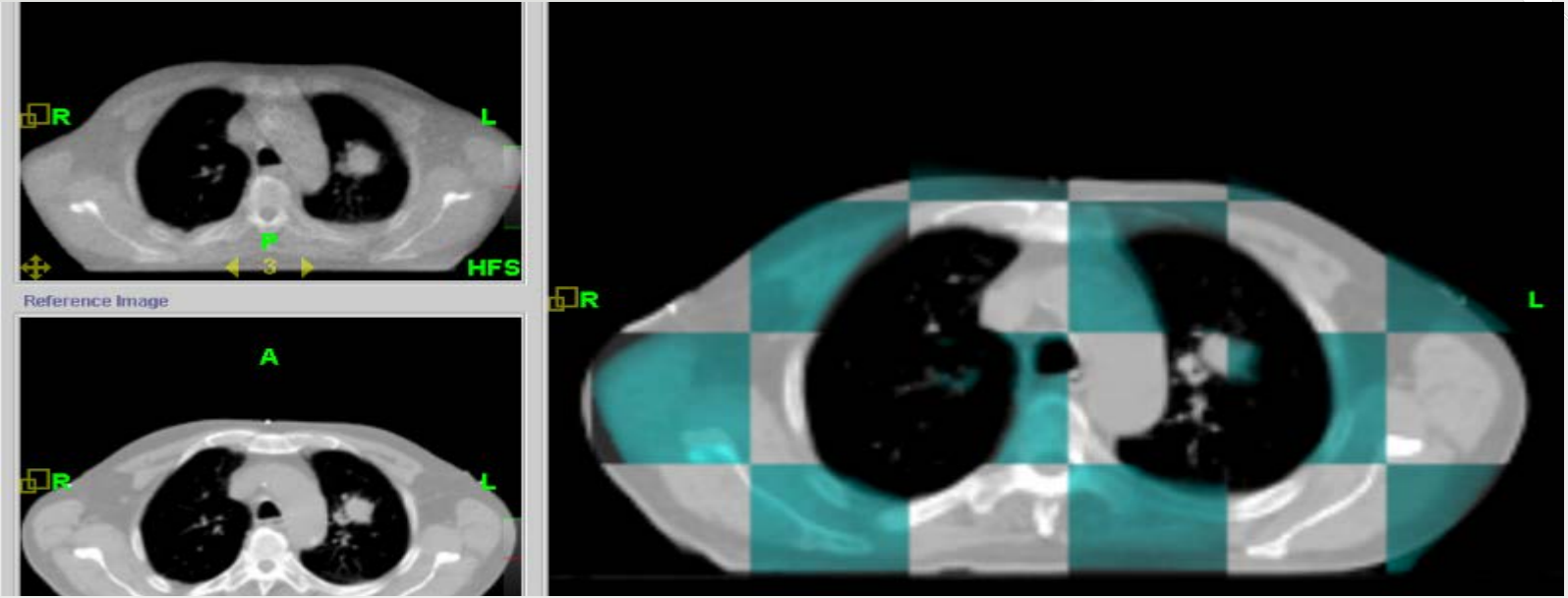
Cette technique associe un accélérateur linéaire de faible énergie qui permet de délivrer la dose par modulation d'intensité, et une tomodensitométrie intégrée qui permet de guider la radiation par imagerie 3D (IGRT).

-Précision de l’ordre du mm

-Réduction de la dose aux tissus sains

Centre intégré
de santé
et de services sociaux
de Laval
Québec

MVCT pour vérification en salle et repositionnement

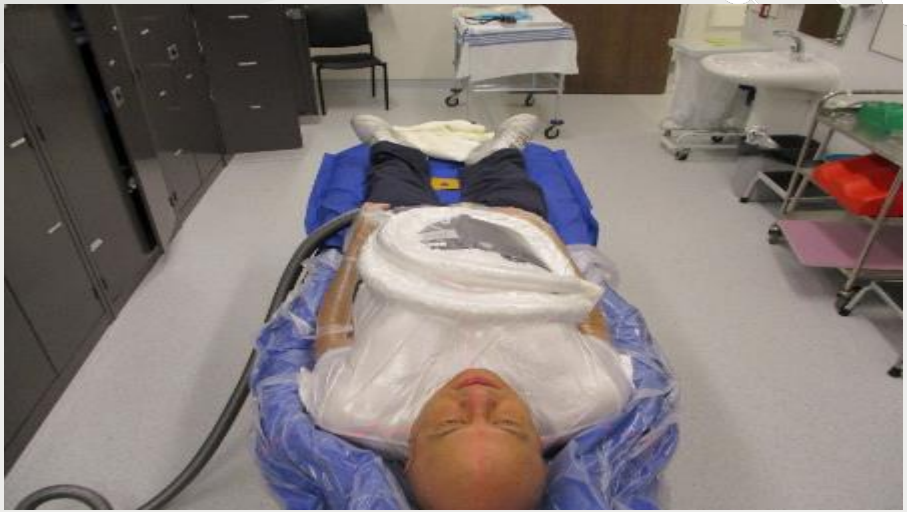


- AAPM Task Group 101
- ASTRO and ACR
- CARO
- National Radiotherapy Implementation Group of the UK

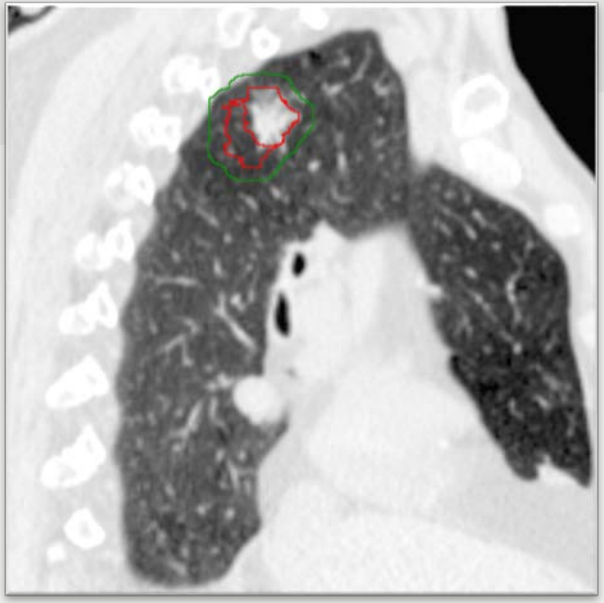
SBRT is **(1)** a method of external beam radiotherapy (EBRT) that **(2)** accurately delivers a **(3)** high dose of irradiation in **(4)** one or few treatment fractions to an **(5)** extracranial target.

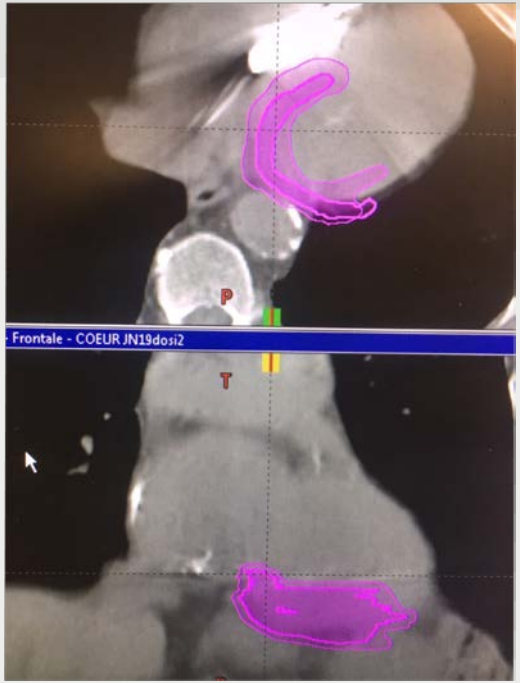
SaBR: stereotactic ablative radiation therapy

Immobilisation pour traitement stéréotaxique corporelle



Planification 4 D et 5D
Incorporer le mouvement pour définir les volumes cibles





Études en cours en radiothérapie

Stade précoce

- Étude Pacific IV
  - Concept de l'immunothérapie
  - Devis de l'étude

- Étude SUNSET
  - Concept de tumeur périphérique, centrale et ultracentrale
  - Devis de l'étude

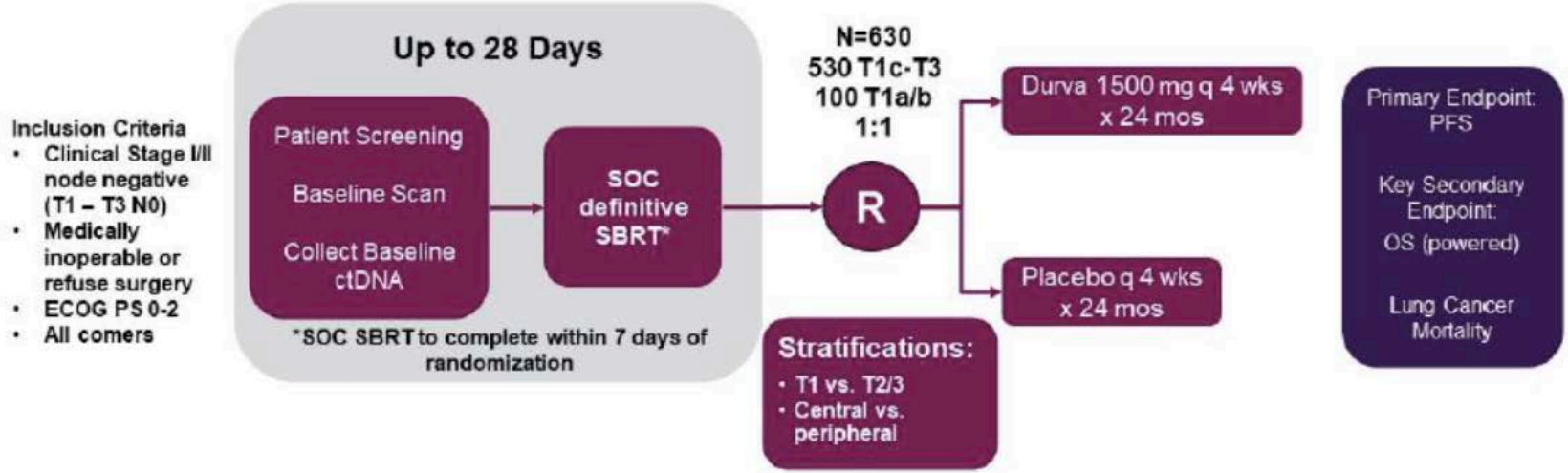
Les récidives post SaBR pour stade précoce sont généralement régionales et à distance

Senthi et al. Lancet 2012

Any LR	30	4%	24%	..	14·9 (11·4–18·4)
Regional recurrence					
Isolated RR	22	3%	18%	..	10·9 (6·1–15·8)
RR and DR	15	2%	12%	..	..
Any RR	43	6%	35%	..	13·1 (7·9–18·3)
Distant recurrence					
Isolated DR	57	8%	46%	..	8·3 (6·4–10·2)
Any DR	82	12%	66%	..	9·6 (6·8–12·4)
Locoregional without DR	42	6%	34%	..	13·1 (9·7–16·5)
Second lung primary					
All	42	6%	..	..	18·0 (12·5–23·5)

NSCLC stade précoce: Pacific IV

Figure 1 **Study design**



ctDNA Circulating tumor DNA; ECOG European Cooperative Oncology Group; mos Months; OS Overall survival; PFS Progression-free survival; PS Performance status; q 4 wks Every 4 weeks; R Randomize; SBRT Stereotactic body radiation therapy; SOC Standard of Care.

DIGNE DE CONFIANCE,
à chaque instant

NSCLC stade précoce: Pacific IV

Éligibilité

I to II NSCLC (American Joint Committee on Cancer Stage [AJCC Cancer Staging Manual, Eighth Edition], with clinical Stage I/II lymph node-negative (T1 to T3N0M0) disease and planned to receive definitive treatment with stereotactic body radiation therapy (SBRT). In order to be eligible for this trial, patients should be

- Medically inoperable as determined by physician or
- Medically operable with patient refusal of surgery
- Patients with medically operable disease who choose to have SBRT are also eligible

6. Completion of standard of care (SoC) SBRT as definitive treatment prior to randomization using one of the following doses:

- For peripheral tumors: 54 Gy total dose delivered in 3 fractions, 42 Gy total dose delivered in 4 fractions, or 50 Gy total dose delivered in 5 fractions
- For central tumors: 50 Gy total dose delivered in 5 fractions

Devis

Administration and Dosing

Durvalumab

1500 mg IV every 4 weeks (q4w)[a]

Placebo

Dosing to match durvalumab[a]

[a] If a patient's weight falls to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo saline solution q4w, as applicable based on treatment assignment, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of 1500 mg durvalumab or placebo saline solution, as applicable based on treatment assignment.

Table 5 Study treatments

	Durvalumab	Placebo
Study treatment name	Durvalumab (MEDI4736)	Saline solution
Dosage formulation	500-mg vial solution for infusion after dilution, 50 mg/mL	Sterile solution of 0.9% (w/v) sodium chloride for injection
Route of administration	IV	IV
Dosing instructions	1500 mg IV q4w[a]	Dosing to match durvalumab[a]
Packaging and labelling	Study treatment will be provided in 500-mg vials. Each vial will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.[b]	Sourced locally by site
Provider	AstraZeneca	Sourced locally by site

[a] If a patient's weight falls to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo saline solution q4w, as applicable based on treatment assignment, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of 1500 mg durvalumab or placebo saline solution, as applicable based on treatment assignment.

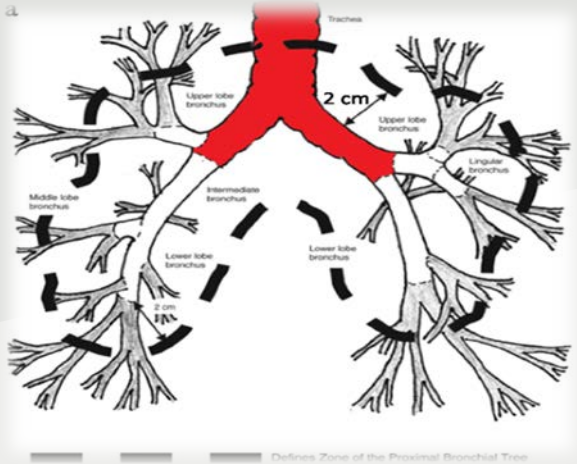
[b] Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

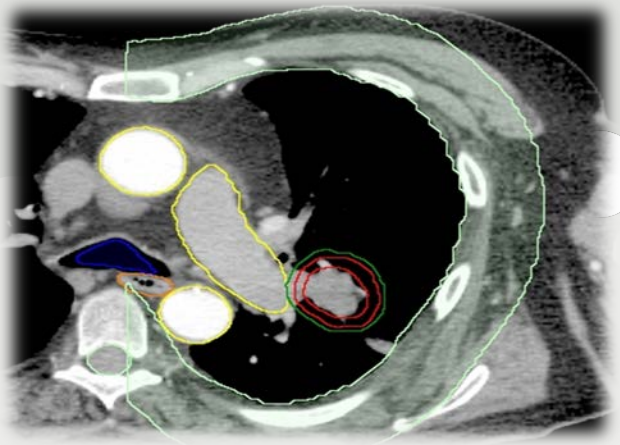
Centre intégré de santé et de services sociaux de Laval
Québec

NSCLC stade précoce: Sunset

Localisation tumorale

- Périphérique
- Centrale
- Ultracentrale





***Central per* RTOG 0813**

≤2 cm to proximal bronchial tree or PTV touching mediastinal/pericardial pleura

Current Trial Report

SUNSET: Stereotactic Radiation for Ultracentral Non–Small-Cell Lung Cancer—A Safety and Efficacy Trial

Meredith Giuliani,[1,2] Ashwathy S. Mathew,[1,2] Houda Bahig,[3] Scott V. Bratman,[1,2] Edith Filion,[3] Daniel Glick,[4] Alexander V. Louie,[5] Srinivas Raman,[1,2] Anand Swaminath,[6] Andrew Warner,[5] Vivian Yau,[1,2] David Palma[5]

- Stage T1-3 N0 M0 NSCLC ≤ 6 cm
- PTV touches or overlaps the central bronchial tree, esophagus, pulmonary vein, or pulmonary artery

- N= 30 patients

Patients with ultra-central NSCLC

T1-3 (≤6 cm) N0 M0

DOSE LEVELS					
	Level -1	Level 0	Level 1	Level 2	Level 3
Dose per fraction:	4 Gy	6 Gy	7.5 Gy	10 Gy	12 Gy
Number of fractions:	15	10	8	6	5
Total Dose:	60 Gy	60 Gy	60 Gy	60 Gy	60 Gy

- Primary endpoint= maximum tolerated dose
  - Dose with ≤ 30% grade 3-5 toxicity within 2 years.

Étude Pacific: Maladie localement avancée

Devis de l'étude: Stade III NSCLC

Objectifs: survie sans progression et survie globale

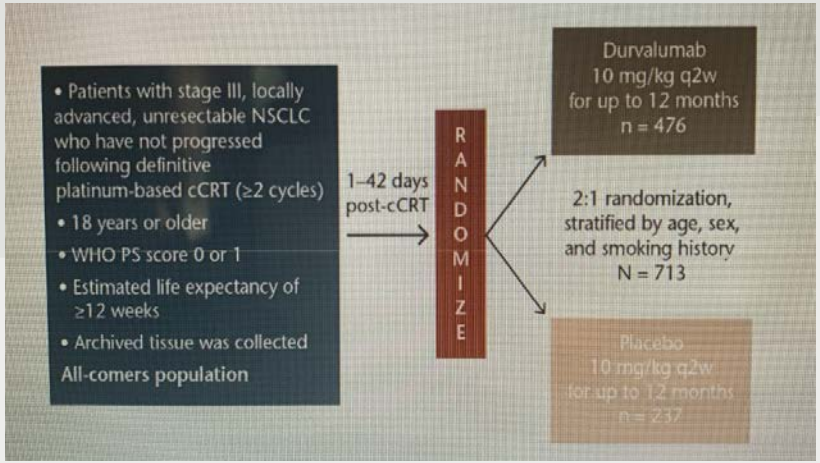
Suivi médian: 3 ans

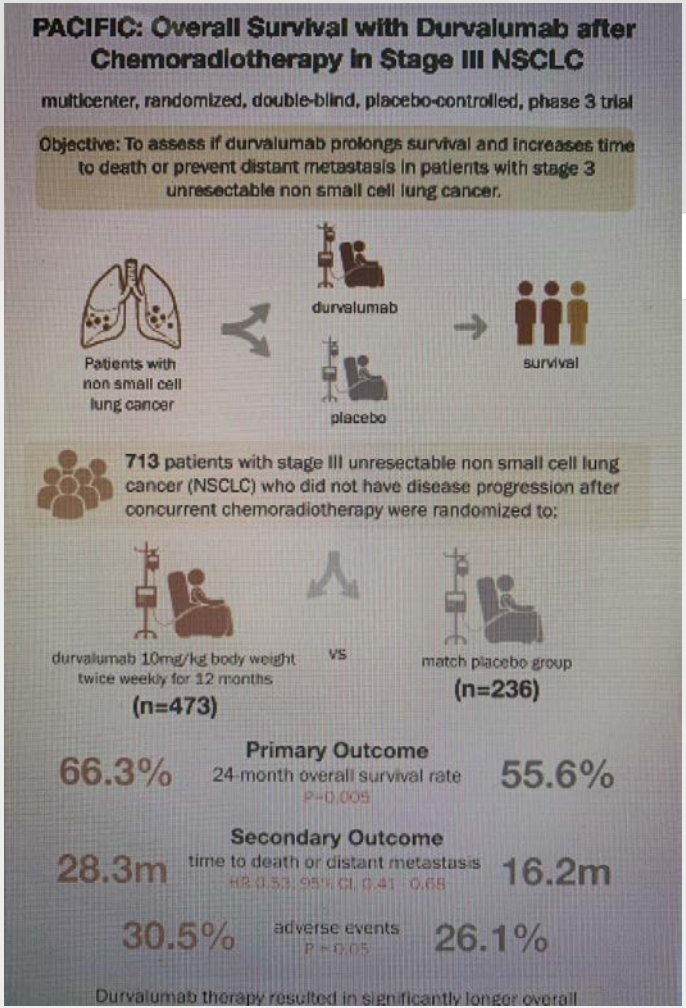
Population: 713 pts, stade III, sans progression apres 2 cycles platine
Durva 476 vs placebo 237

Résultats: Survie à 3 ans 57 % vs 43.5 %

DIGNE DE CONFIANCE,
à chaque instant

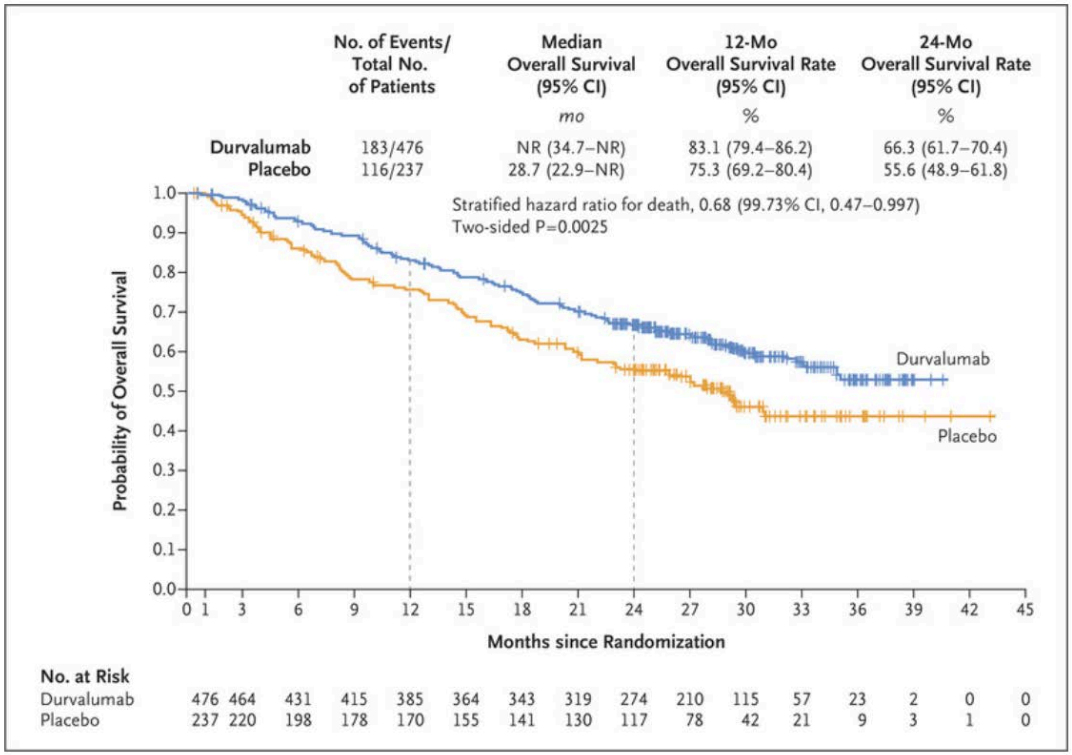
Étude PACIFIC





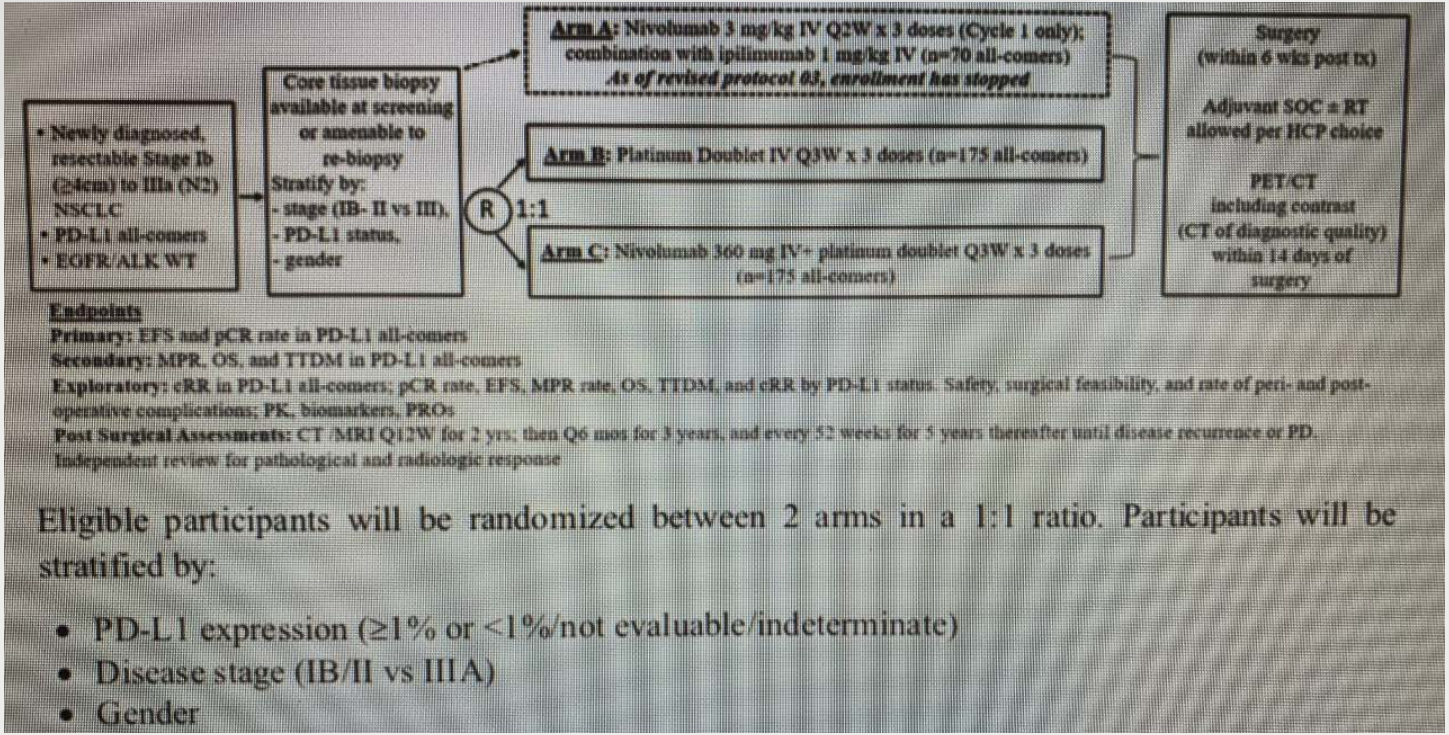
Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

Scott J. Antonia, M.D., Ph.D., Augusto Villegas, M.D., Davey Daniel, M.D., David Vicente, M.D., Shuji Murakami, M.D., Rina Hui, Ph.D., Takayasu Kurata, M.D., Ph.D., Alberto Chiappori, M.D., Ki H. Lee, M.D., Ph.D., Maike de Wit, M.D., Ph.D., Byoung C. Cho, M.D., Ph.D., Maryam Bourhaba, M.D., et al., for the PACIFIC Investigators*



Études en cours en radiothérapie

Stade localement avancé



Approche en contexte métastatique

- 50% NSCLC M+ au diagnostic

- Historiquement
  - Thérapies systémiques visant à retarder la progression et à prolonger la vie

- Paradigme oligométastatique
  - Fenêtre d'opportunité chez patients avec un nombre limité de métastases?

Étude SaBR-COMET

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek,

Lancet 2019

Devis de l'étude:SaBR

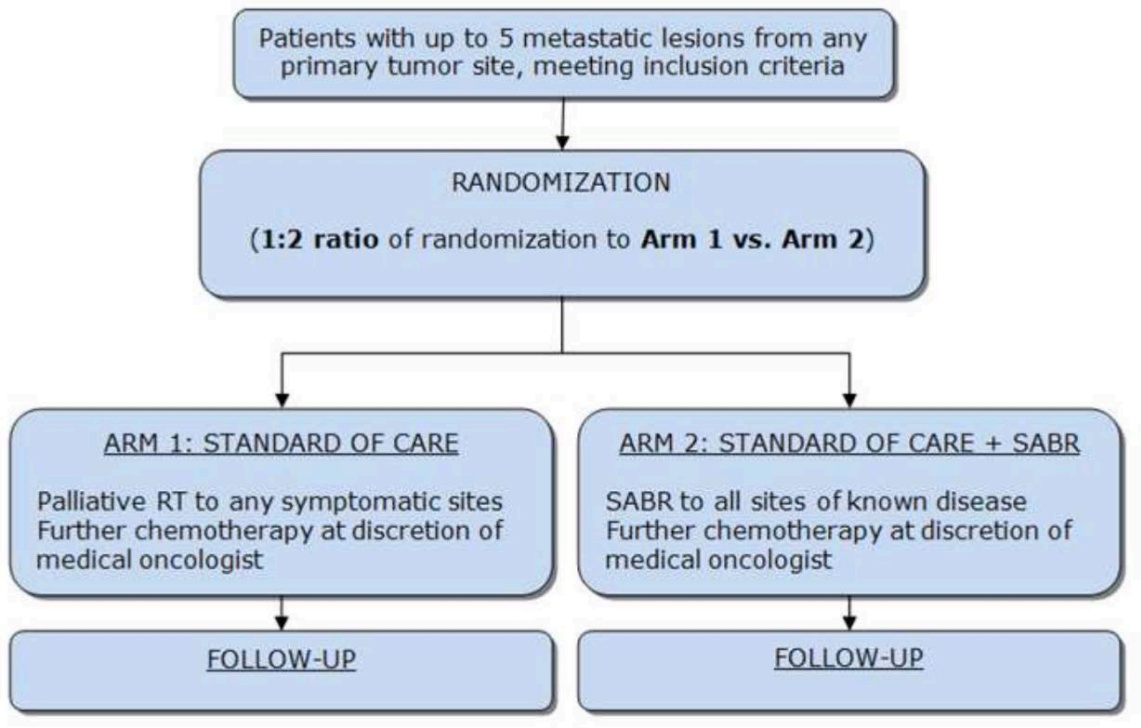
Étude multicentrique phase 2

Px de plus de 6 mois, ECOG 0-1, (sein, pms, coloR, prostate)

Tx palliatif vs SabR

FU médian 27 mois

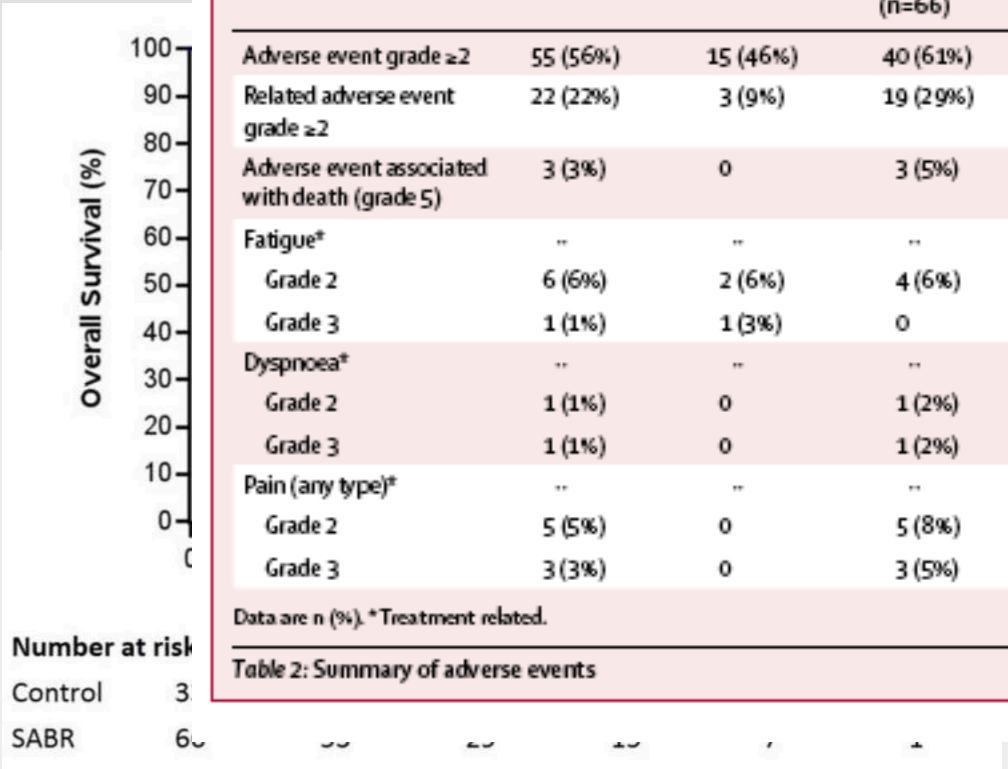
Approche en contexte métastatique
Étude SABR-COMET



Palma et al. Astro 2018

DIGNE DE CONFIANCE,
Actualités.ca

Augmentation de la survie avec radiothérapie stéréotaxique sur jusqu'à 5 lé



	All patients (n=99)	Control group (n=33)	Stereotactic ablative radiotherapy group (n=66)	p value
Adverse event grade ≥2	55 (56%)	15 (46%)	40 (61%)	0·15
Related adverse event grade ≥2	22 (22%)	3 (9%)	19 (29%)	0·026
Adverse event associated with death (grade 5)	3 (3%)	0	3 (5%)	0·55
Fatigue*	..	..	..	0·45
Grade 2	6 (6%)	2 (6%)	4 (6%)	..
Grade 3	1 (1%)	1 (3%)	0	..
Dyspnoea*	..	..	..	1·00
Grade 2	1 (1%)	0	1 (2%)	..
Grade 3	1 (1%)	0	1 (2%)	..
Pain (any type)*	..	..	..	0·14
Grade 2	5 (5%)	0	5 (8%)	..
Grade 3	3 (3%)	0	3 (5%)	..

Data are n (%). *Treatment related.

Table 2: Summary of adverse events

édiane
trol: 28 mois
mois

Centre intégré de santé et de services sociaux de Laval
Québec

Message clé

Survie médiane 41 mois (SaBR) vs 28 mois(groupe standard)

Survie sans progression 12 mois (SaBR) vs 6 mois (standard)

30 % ES de grade 2 et plus (SaBR) vs 9% (standard)
(plus de toxicités mais QOL idem)

A venir étude COMET II: phase III pour 1-3 et 4-10 lésions métastatiques

The « OLI*GOMEZ* » Trial

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

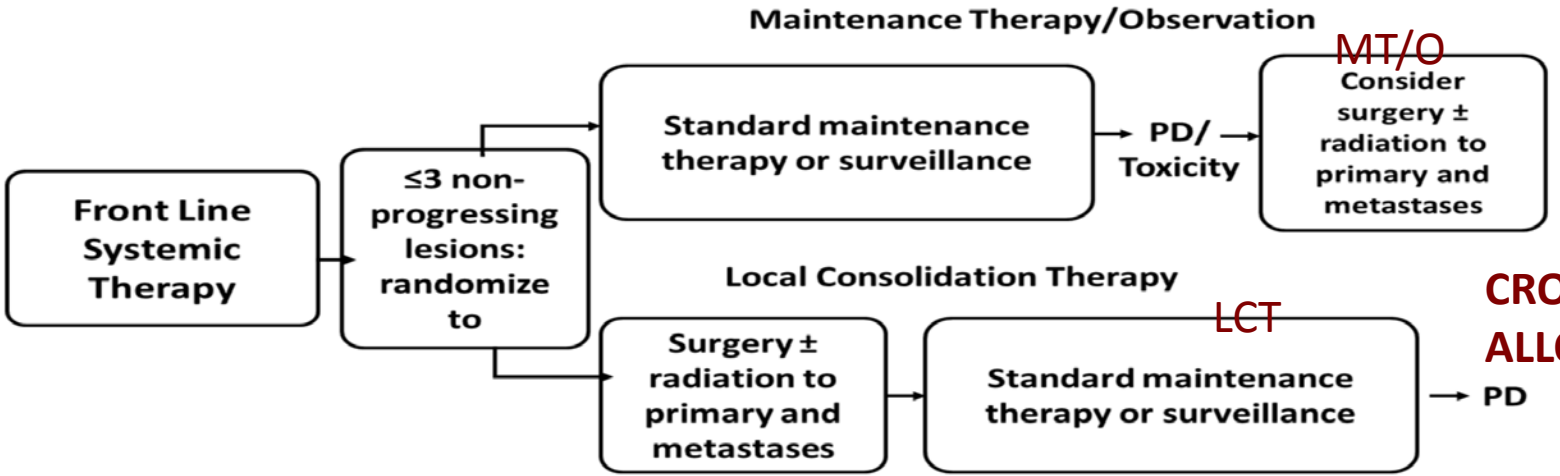
Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher, John V Heymach**

Lancet Oncol 2016; 17: 1672–82
Published Online
October 24, 2016
http://dx.doi.org/10.1016/
S1470-2045(16)30532-0

Summary

Background Evidence from retrospective studies suggests that disease progression after first-line chemotherapy for metastatic non-small-cell lung cancer (NSCLC) occurs most often at sites of disease known to exist at baseline. However, the potential effect of aggressive local consolidative therapy for patients with oligometastatic NSCLC is unknown. We aimed to assess the effect of local consolidative therapy on progression-free survival.

- Inclusion criteria:
  - stage IV disease NSCLC
  - 1–3 metastatic lesions (counted after 1st line systemic therapy)
  - 1st line systemic treatment
- Target randomization = 94 patients ➔ early closure at 49 patients
- Primary endpoint: PFS



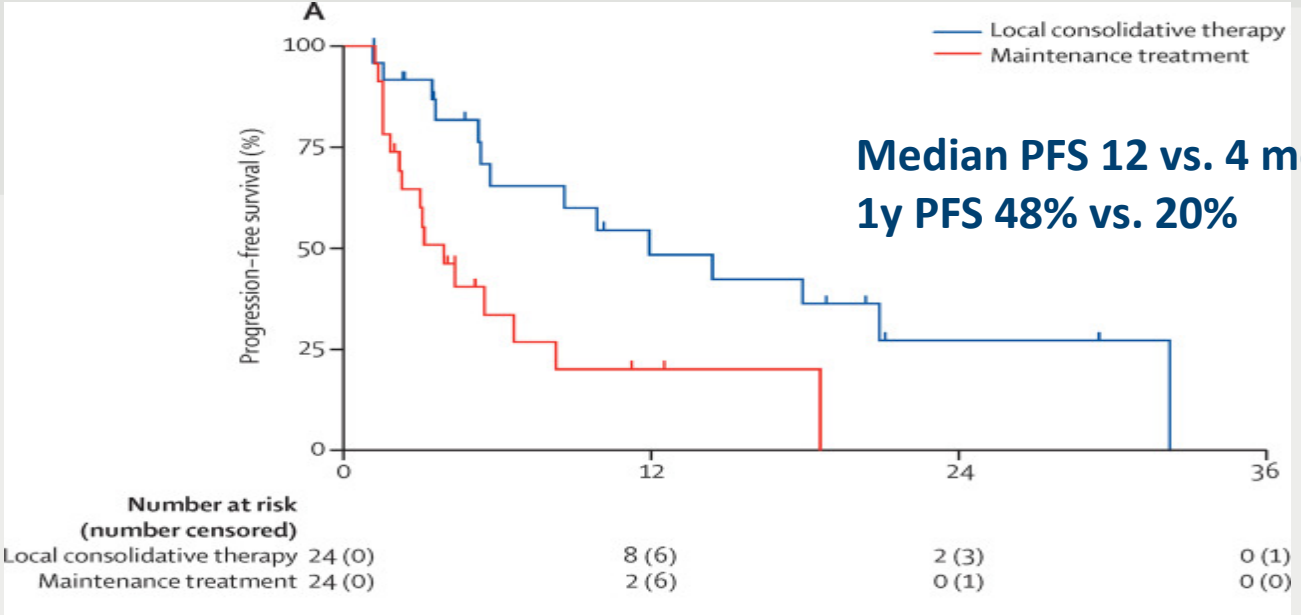
Obj. 1er : PFS
(power to detect difference
4 mo MT/O vs. 7 mo LCT, n=94)

Obj.secondaires : OS, toxicités

Balanced for:
- Nb of mets (0-1 vs. 2-3)
- Response to systemic treatment
- N0-1 vs. N2-3
- CNS mets vs No
- EGFR/ALK vs. No

Early closure after 49/94 patients

- Median follow-up was 12 months
  13 months LCT vs. 11 months maintenance



Median PFS 12 vs. 4 mo (p=0.005)
1y PFS 48% vs. 20%

Local Consolidative Therapy Vs. Maintenance

RESULTS The Data Safety and Monitoring Board recommended early trial closure after 49 patients were randomly assigned because of a significant PFS benefit in the LCT arm. With an updated median follow-up time of 38.8 months (range, 28.3 to 61.4 months), the PFS benefit was durable (median, 14.2 months [95% CI, 7.4 to 23.1 months] with LCT *v* 4.4 months [95% CI, 2.2 to 8.3 months] with MT/O; $P = .022$). We also found an OS benefit in the LCT arm (median, 41.2 months [95% CI, 18.9 months to not reached] with LCT *v* 17.0 months [95% CI, 10.1 to 39.8 months] with MT/O; $P = .017$). No additional grade 3 or greater toxicities were observed. Survival after progression was longer in the LCT group (37.6 months with LCT *v* 9.4 months with MT/O; $P = .034$). Of the 20 patients who experienced progression in the MT/O arm, nine received LCT to all lesions after progression, and the median OS was 17 months (95% CI, 7.8 months to not reached).

Jose A. Karam, MD[1]; Brian D. Kavanagh, MD, MPH[3]; Anne S. Tsao, MD[1]; Boris Sepesi, MD[1]; Stephen G. Swisher, MD[1]; and John V. Heymach, MD, PhD[1]

Clin Oncol 37:1558-1565. © 2019 by American Society of Clinical Oncology

Median f/u 39 mo

PFS 14.2 vs. 4.4 mo (p=0.02)

Median OS:41 vs. 17 mo (p=0.017)

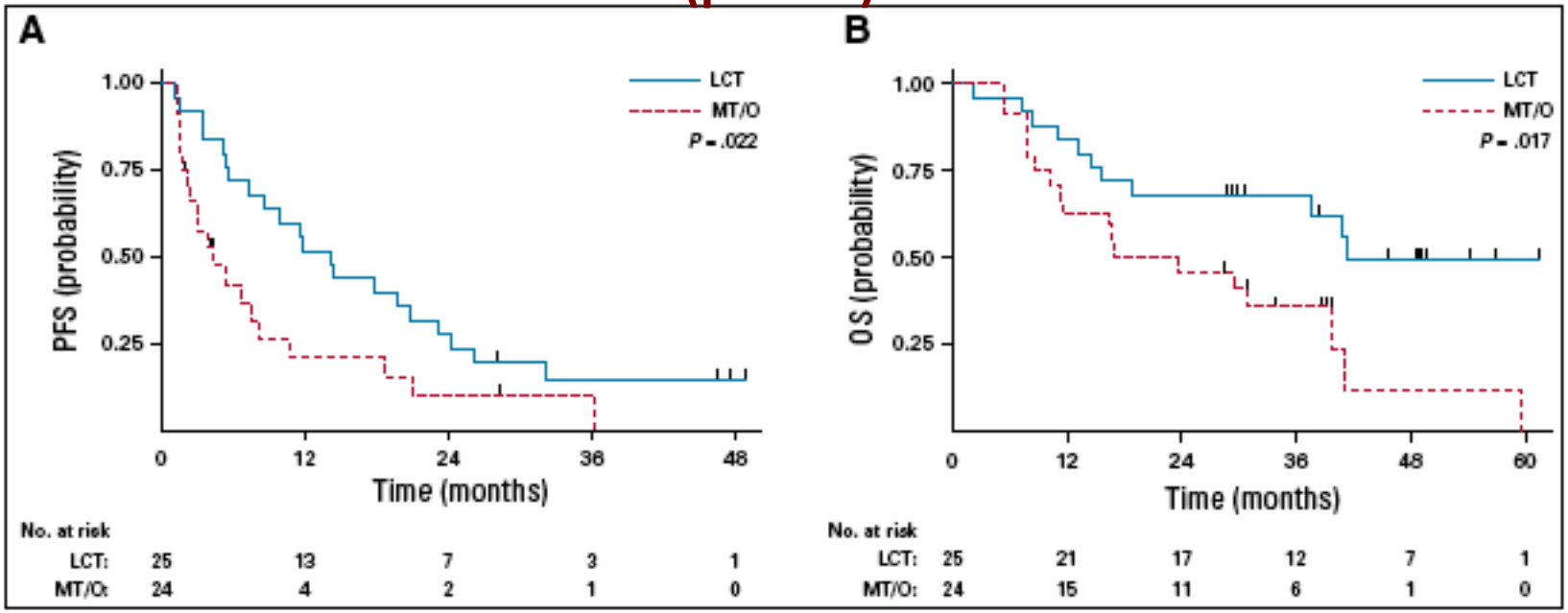


FIG 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non–small-cell lung cancer.

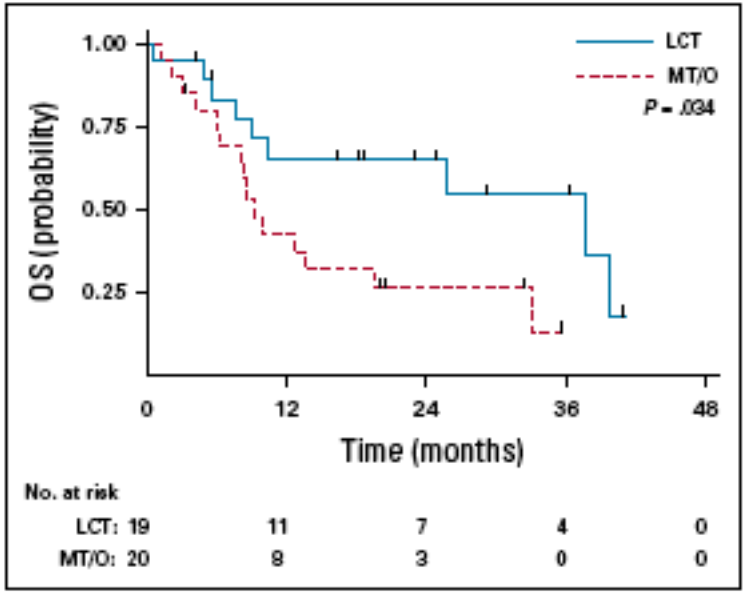


FIG 2. Overall survival (OS) after disease progression among patients originally assigned to local consolidative therapy (LCT) or maintenance therapy or observation (MT/O).

TABLE 2. Summary of Multivariable Cox Proportional Hazards Model That Includes Treatment Arm, Number of Metastases, and *ALK/EGFR* Alteration

Variable	HR	95% CI	P
Treatment			
MO	Ref		
LCT	0.46	(0.21 to 0.99)	.048
No. of metastases			
1	Ref		
2-3	1.50	(0.69 to 3.26)	.310
Mutation status			
None	Ref		
EGFR/EML4ALK	0.15	(0.02 to 1.12)	.065

Abbreviations: HR, hazard ratio; MO, maintenance therapy or observation; Ref, reference; LCT, local consolidative therapy.

« Oligomez » Toxicity

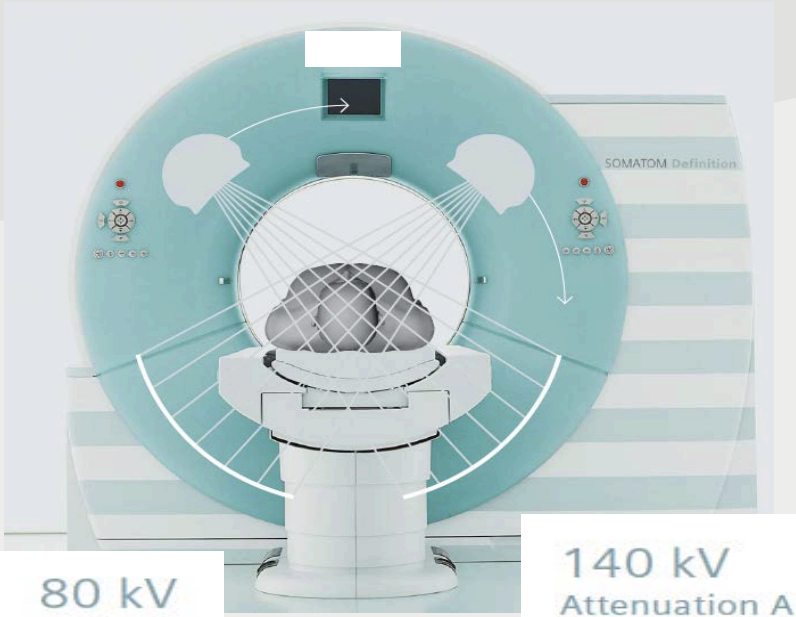
- *Gomez et al. Lancet 2016*
  - 5/25 patients in LCT group with grade 3 toxicities
  - 2/24 patients in MT/O group with grade 3 toxicities
  - No grade 4

- No additional toxicities in JCO 2019 update

- Nouveautés techniques en radiothérapie
- Concepts d’avenir

DIGNE DE CONFIANCE,
à chaque instant

Planification
Imagerie fonctionnelle – Le CT à double énergie



2 tubes à rayon-X de voltage différents

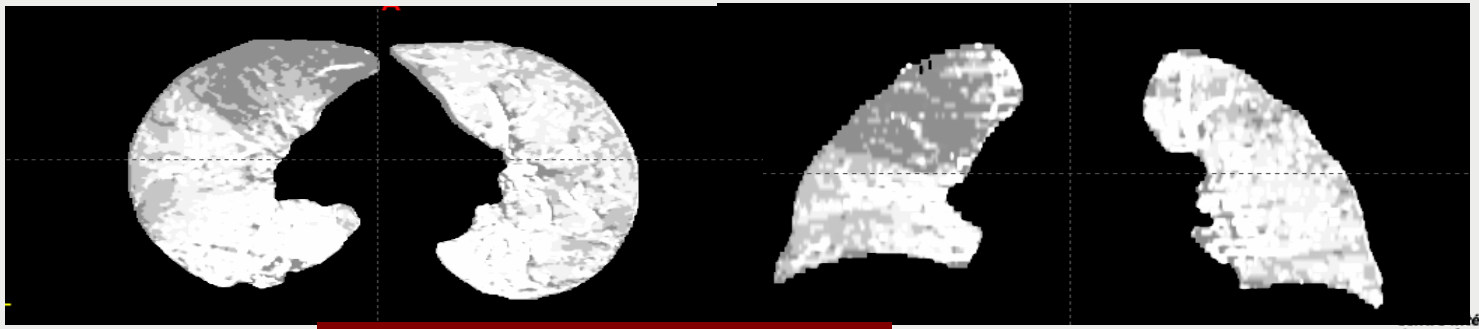
Quantification de la concentration d'iode

http://www.varian.com/dyna/varian-siemens

CHUM

Planification
Imagerie fonctionnelle – Carte d'iode du CT à double énergie

- Extraction de la distribution d'iode sur le DECT
- Pondération attribuée à chaque voxel de parenchyme, basée sur concentration d'iode
  - Contribution relative de chaque voxel à la fonction totale.



Cartographie d'iode

H Bahig

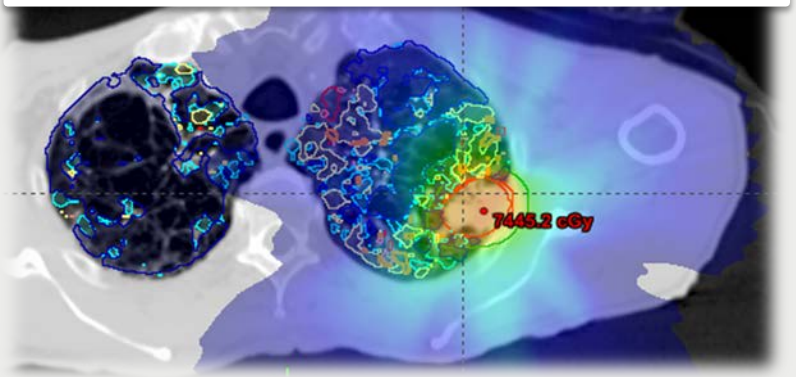
DIGNE DE CONFIANCE,
à chaque instant

Planification

Imagerie fonctionnelle pour minimiser les toxicités de la RT

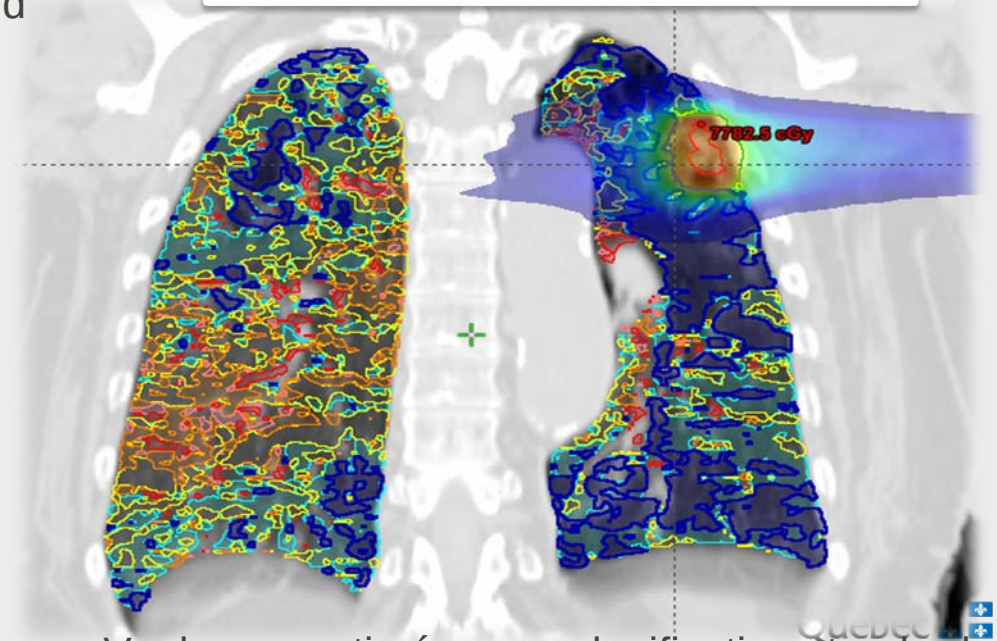
Vpulm sous estimés avec planification standard

V20= 4% vs. fV20= 7%
V5= 10% vs. fV5 = 20%



H Bahig

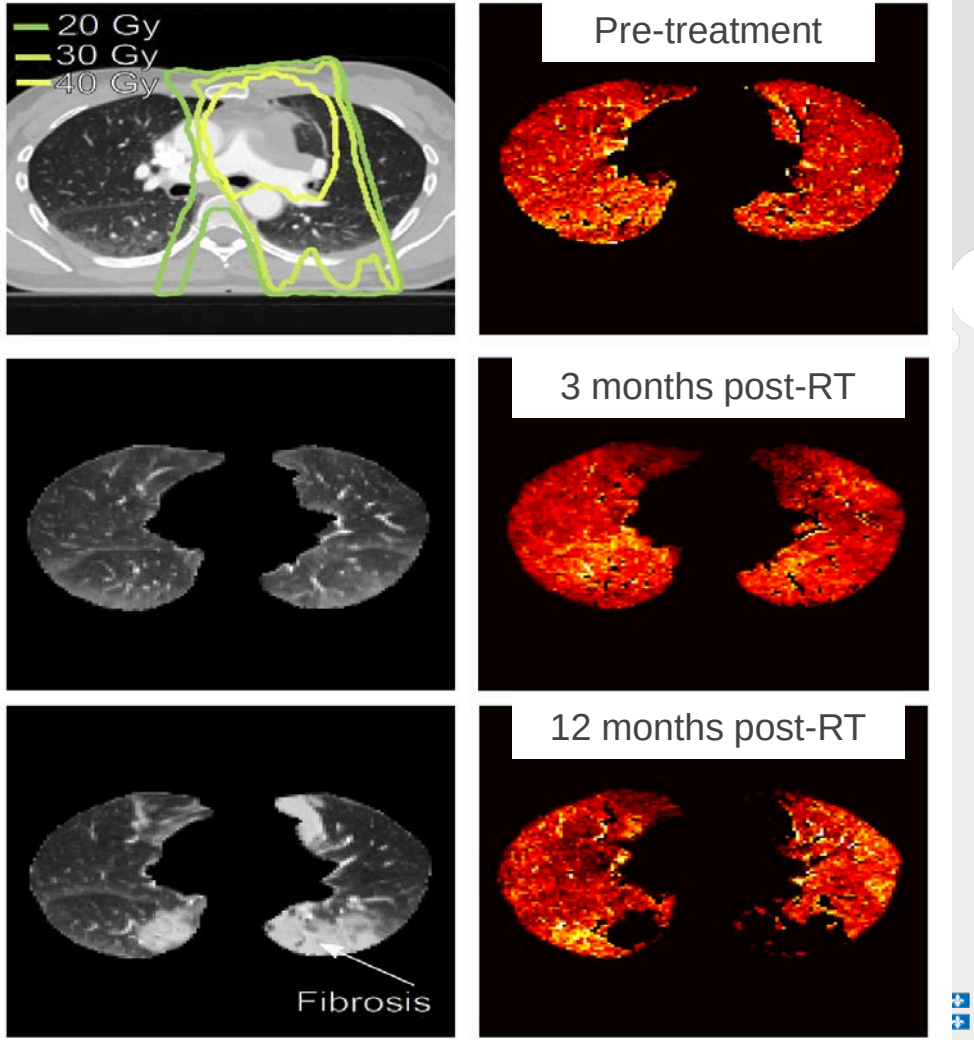
V5= 10% vs. fV5= 5%



Vpulm sur estimés avec planification standard

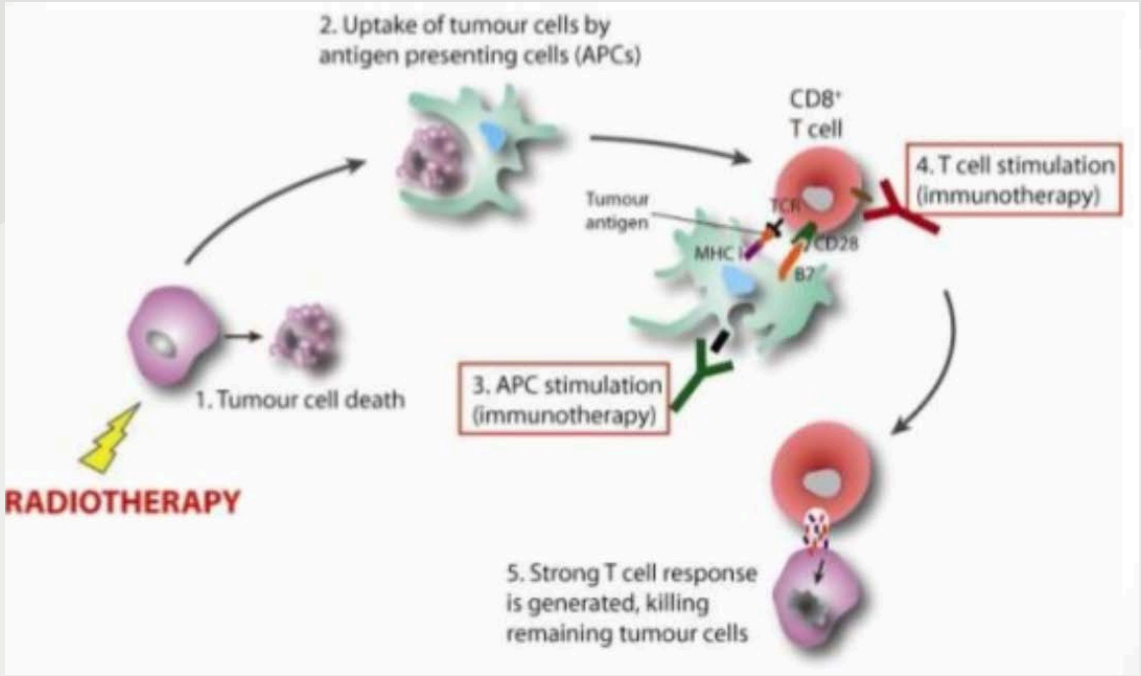
DIGNE DE CONFIANCE,
à chaque instant

Évaluation des changements au parenchyme pulmonaire post traitement



Lapointe et al. Med Phys 2017

Décision de traitement
Immunothérapie combinée à RT



- **PD-1 inhibitors**

-Pembrolizumab (Keytruda)
-Nivolumab (Opdivo)
-Cemiplimab (Libtayo)

- **PDL-1 inhibitors**

-Atezolizumab (Tecentriq)
-Durvalumab (Imfinzi)
-Avelumab (Bavencio)

Radiothérapie

1. Recrutement des cellules T dans le microenvironment tumoral
2. Sécretion de cytokines
3. Présentation d'antigènes

Gorby Castillo, 2017

Conclusion

- Avancées informatiques, technologiques et scientifiques permettent d'offrir de meilleurs traitements à nos patients

- Personalisation et traitement adapté à la radiobiologie de la tumeur et de l'évolution naturelle de la maladie

- Message d'espoir aux patients dans la quête contre le cancer pulmonaire

DIGNE DE CONFIANCE,
à chaque instant

Merci de votre attention

Remerciements particuliers à l'équipe thoracique et physique au CHUM

edith.filion.chum@ssss.gouv.qc.ca
514-890-8254

Centre intégré
de santé
et de services sociaux
de Laval
Québec