Introduction à la radiothérapie
UE 19 - item 294 / 291

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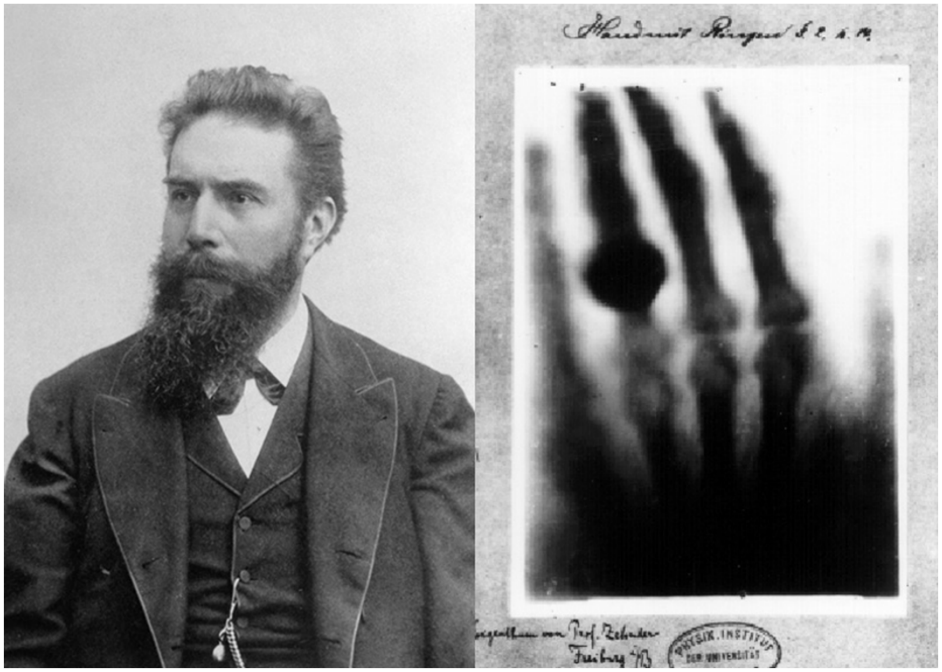
Introduction

A

Les Rayons X

Découverte des Rayons X par Conrad Roentgen fin 1895.
Utilisés à toutes sortes de fins, médicales et non médicales, de nombreux accidents sont rapportés dès 1896, puis des cancers de la peau un peu plus tard.



1845-1923

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Une des premières radiographies…

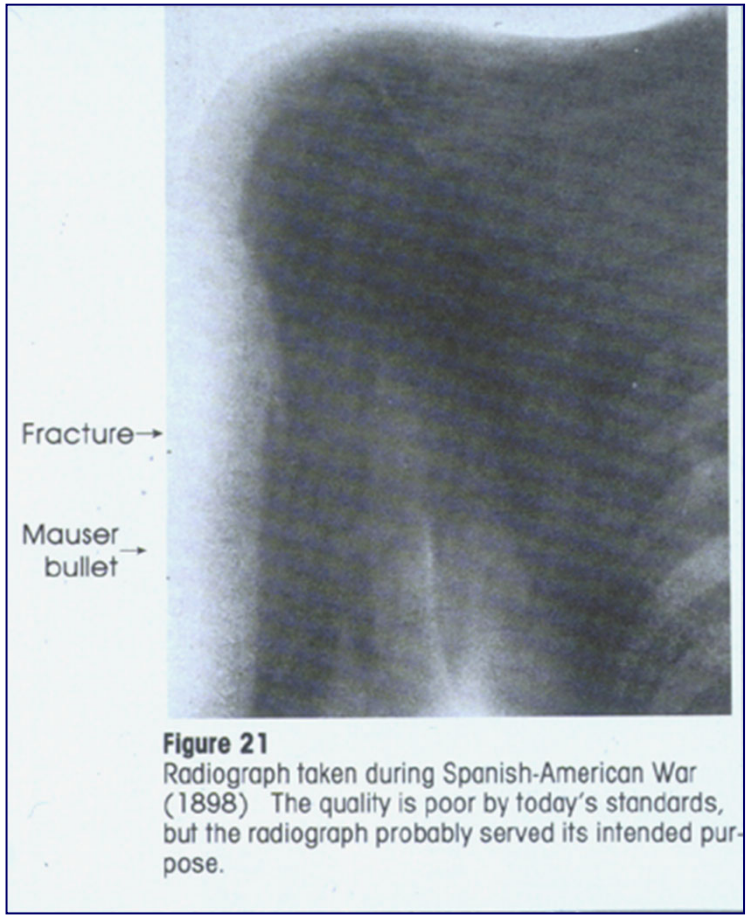


Figure 21
Radiograph taken during Spanish-American War (1898) The quality is poor by today's standards, but the radiograph probably served its intended purpose.

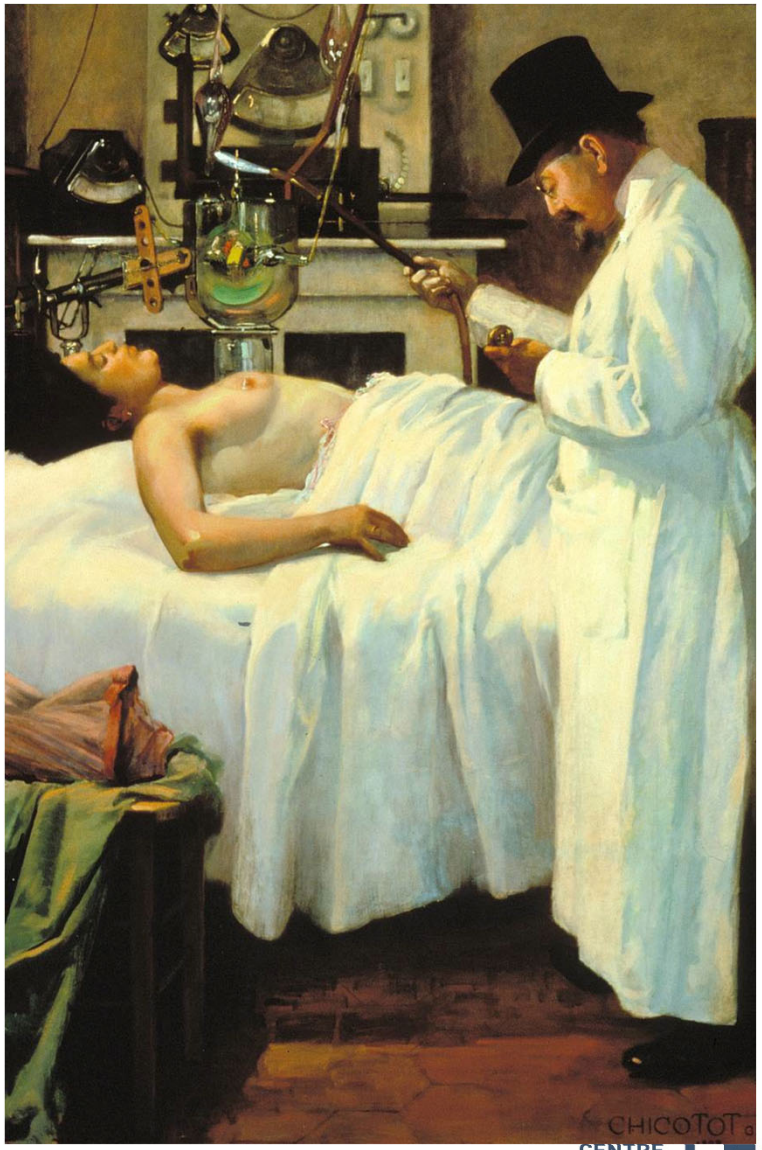
Figure 22
Radiation injury to the skin of a Spanish-American War soldier as a result of an x-ray examination (1898)

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

C

Rayons X

Découverts en 1895 et immédiatement appliqués au traitement du cancer.
Pourquoi?
Parce que la chirurgie était la seule option, et elle était dangereuse…



CENTRE DE LUTTE CONTRE LE CANCER LÉON BERARD

C

Utilisation thérapeutique des Rayons-X

Victor Despeignes (1866 - 1937)

Et à Lyon…?

1er traitement par Rx en 1896 pour un lymphome (?) gastrique

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

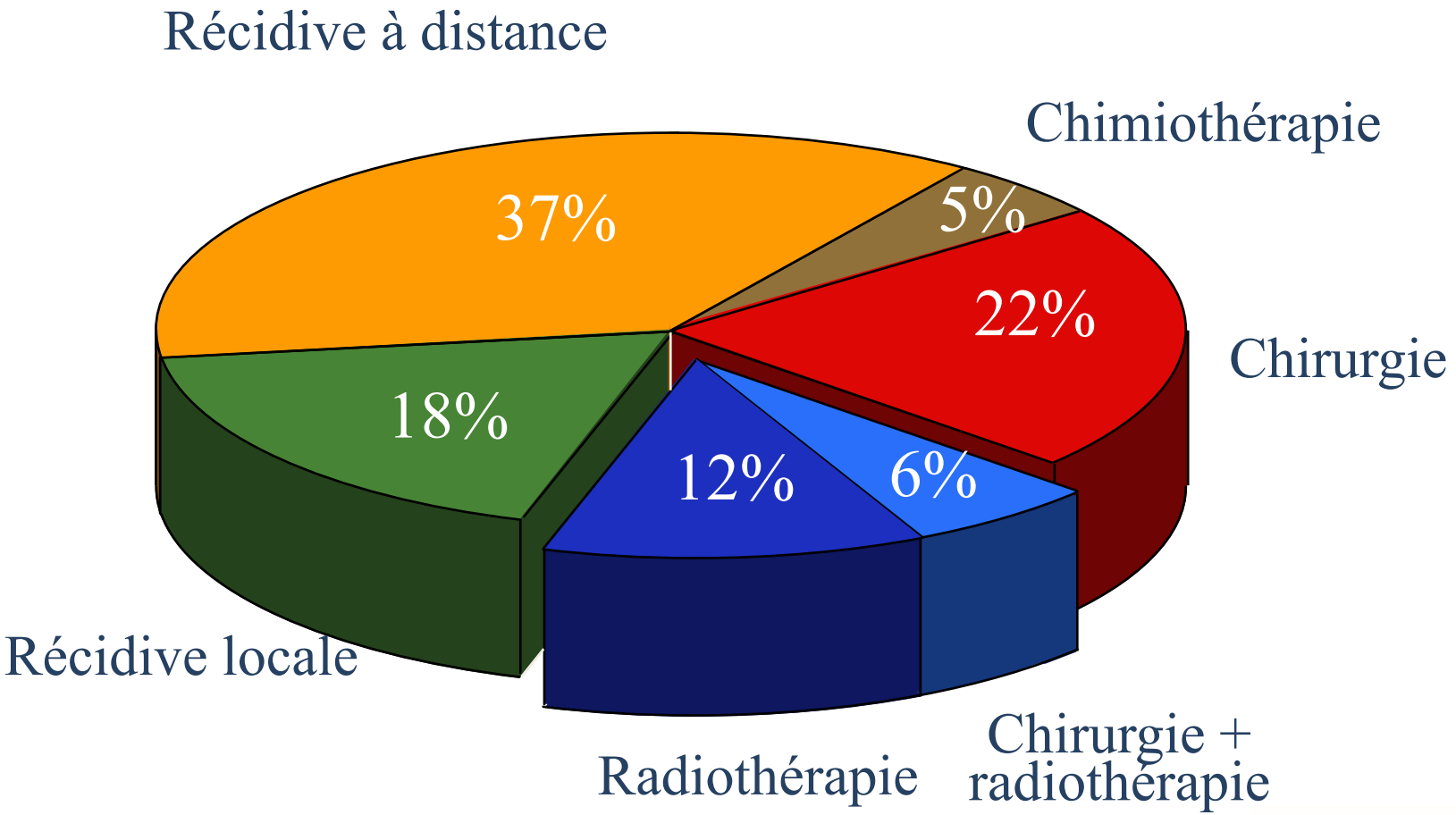
La radiothérapie en 2019 en quelques chiffres

- 385.000 nouveaux cas estimés de cancer en 2019 en France métropolitaine
- 46.000 cancers en région Auvergnes-Rhône-Alpes
- 50-60% bénéficieront d'un traitement par radiothérapie à visée curative ou palliative

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

Faits et mythes en oncologie



CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

Types of ionizing radiation

- Electromagnetic radiation (low LET): photons, g-rays, X-rays
- Particulate Radiation(high LET)
  - charged particles: electrons, protons, a particles
  - neutrons
  - heavy charged ions: carbon, neons, argon, …

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

B

Quantities and units

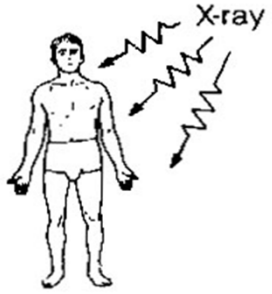
Absorbed dose: 1 Gray (Gy) = 1 joule/kg

= increase of 0.0001 °C per gr water

Total-Body Irradiation

Mass = 70 kg
LD/50/60 = 4 Gy
Energy absorbed =

$$70 \times 4 = 280 \text{ joules}$$
$$= \frac{280}{4.18} = 67 \text{ calories}$$



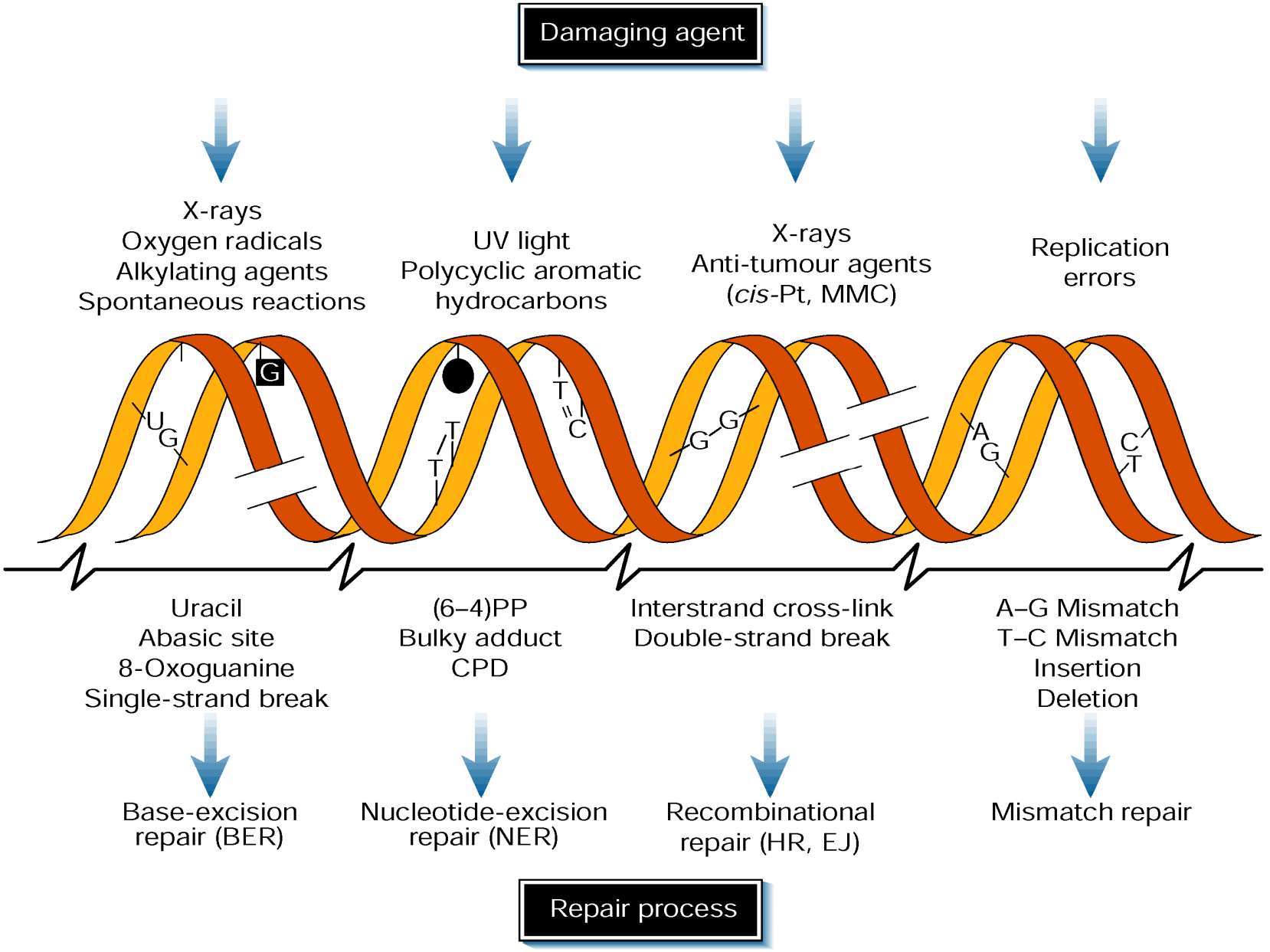
Drinking Hot Coffee

Excess temperature (°C) = 60° − 37° = 23°
Volume of coffee consumed to equal the energy in the LD/50/60 = $\frac{67}{23}$
= 3 mL
= 1 sip

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Biological bases of radiotherapy

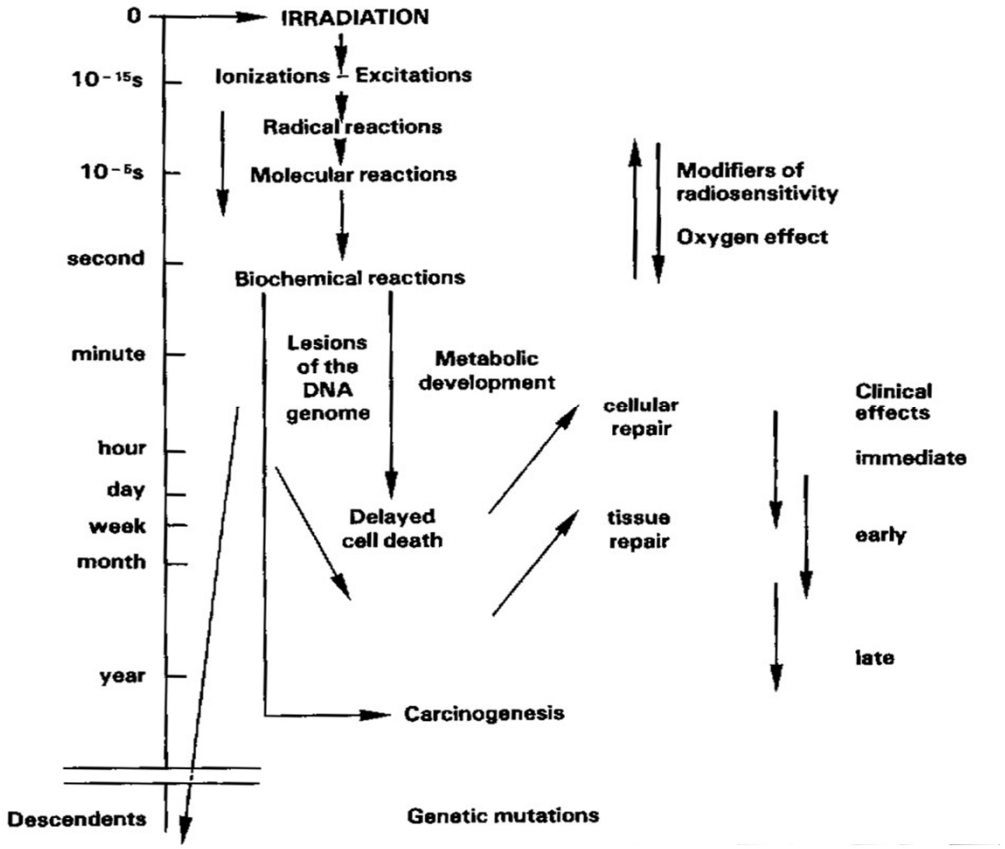
B


Damaging agent
X-rays
Oxygen radicals
Alkylating agents
Spontaneous reactions
UV light
Polycyclic aromatic
hydrocarbons
X-rays
Anti-tumour agents
(cis-Pt, MMC)
Replication
errors
U
G
G
T
T
T
C
G
G
A
G
C
T
Uracil
Abasic site
8-Oxoguanine
Single-strand break
(6–4)PP
Bulky adduct
CPD
Interstrand cross-link
Double-strand break
A–G Mismatch
T–C Mismatch
Insertion
Deletion
Base-excision
repair (BER)
Nucleotide-excision
repair (NER)
Recombinational
repair (HR, EJ)
Mismatch repair
Repair process

B

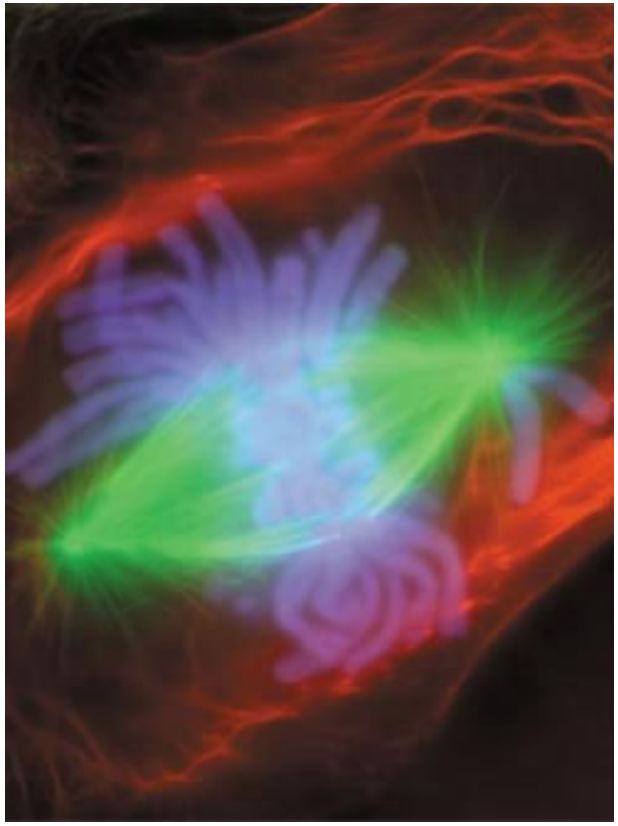
The physics and chemistry of radiation absorption

Chronology of events



B

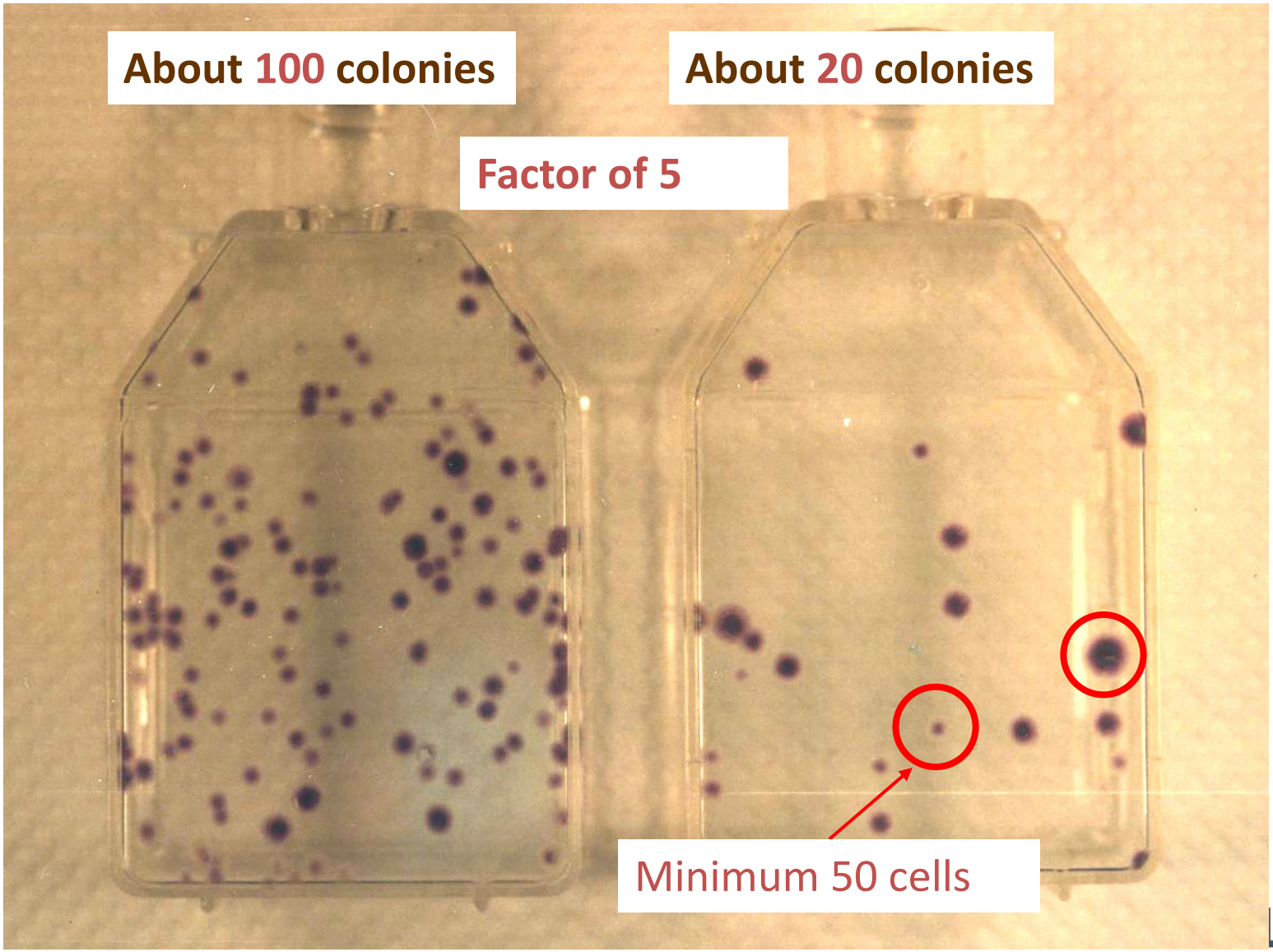
Effects of irradiation on mitosis



Effects on mitosis in plant cells:
endosperm of Haemanthus - time-lapse movie A. Bajer (1962)

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

B

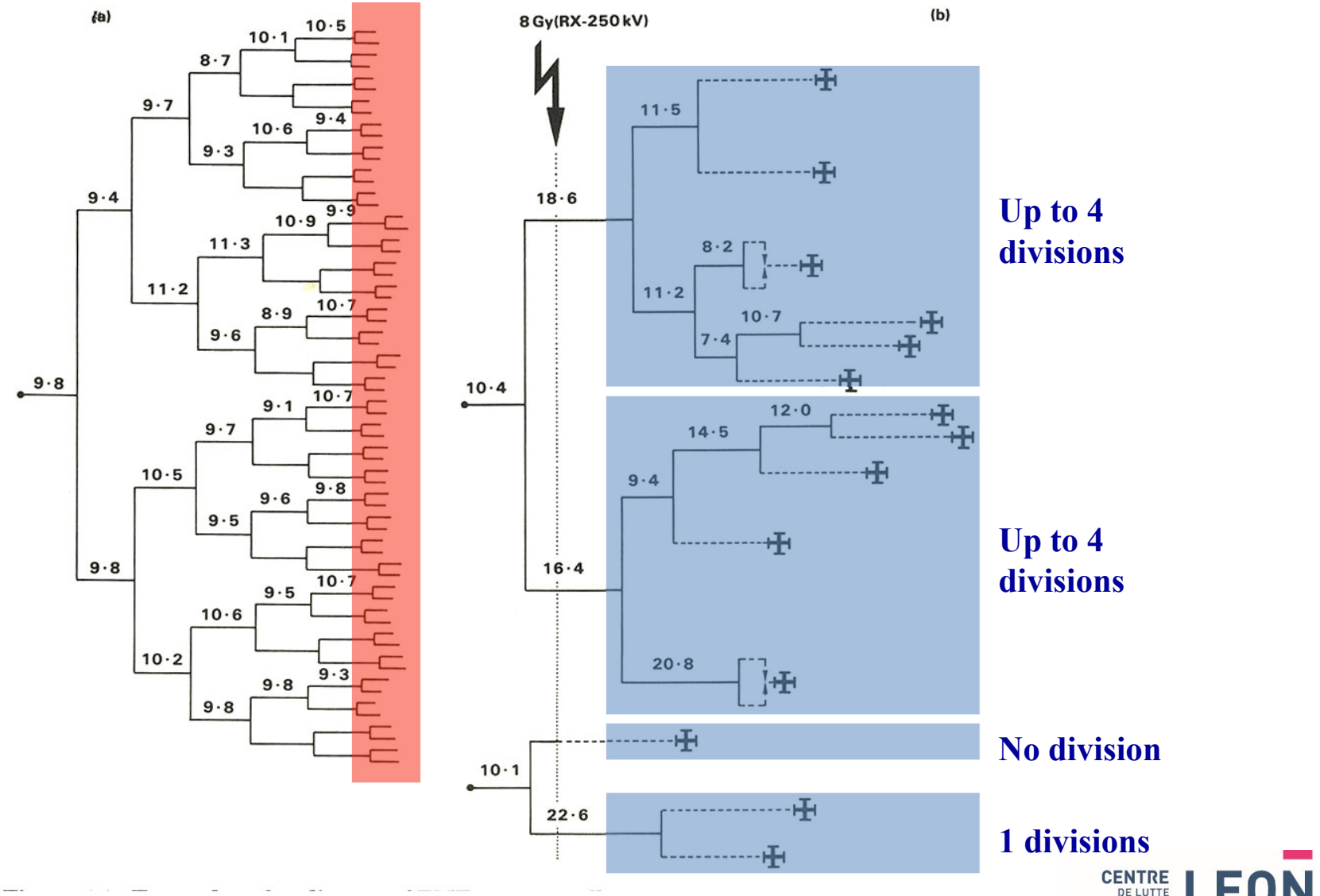


LEON BERARD

A

Unirradiated cells

Irradiated cells



Up to 4 divisions

Up to 4 divisions

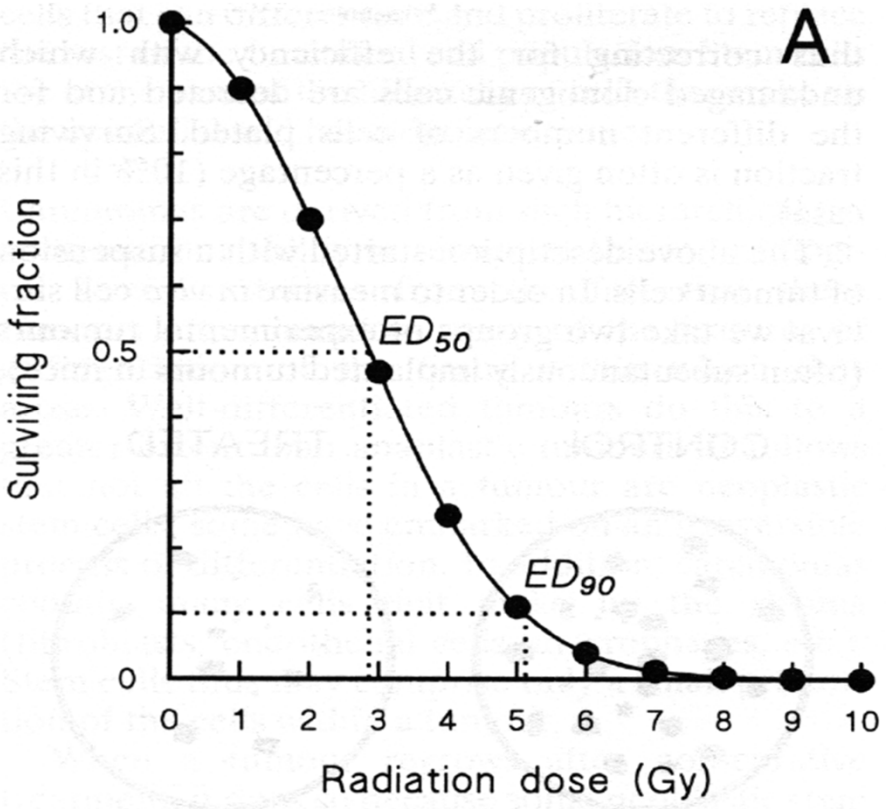
No division

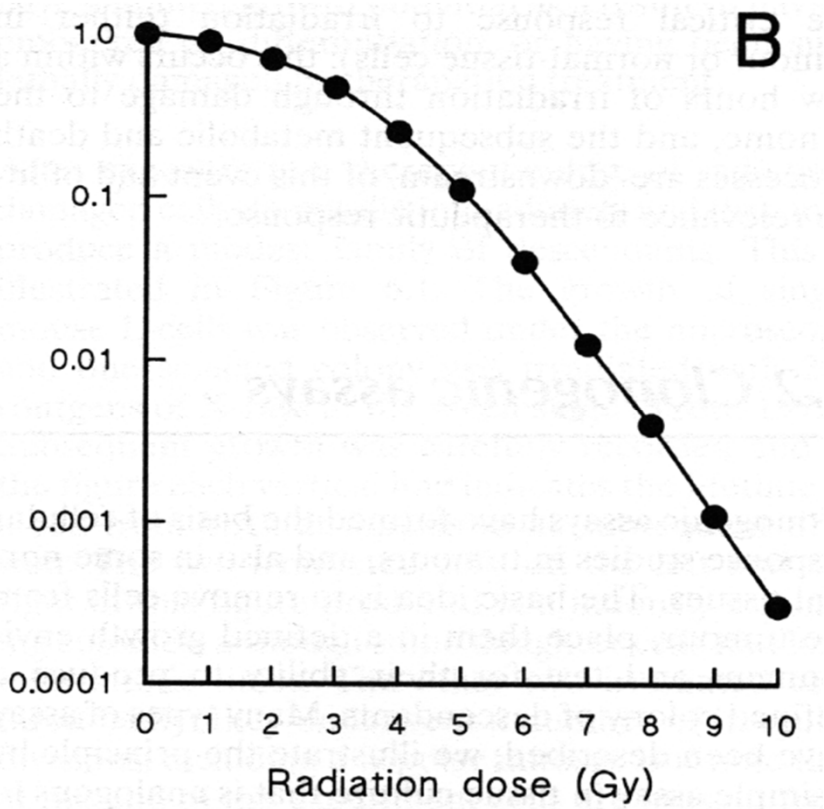
1 divisions

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

B

Cell survival curves





CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

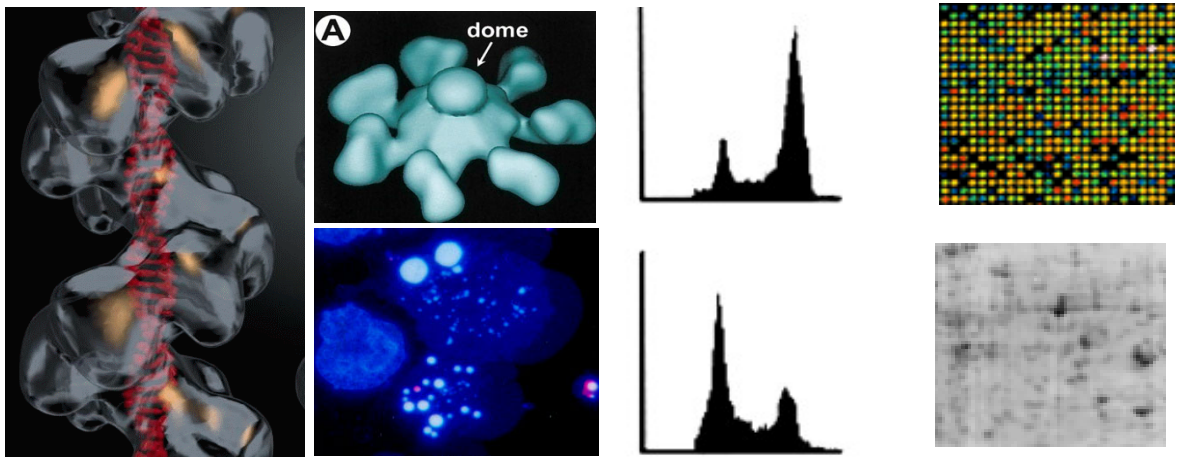
B

Initial cellular responses to radiation

Sensors of damage

Biological Pathways

DNA Repair	Early Apoptosis	Cell cycle checkpoints	Gene expression



CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

B

HR and Human Disease

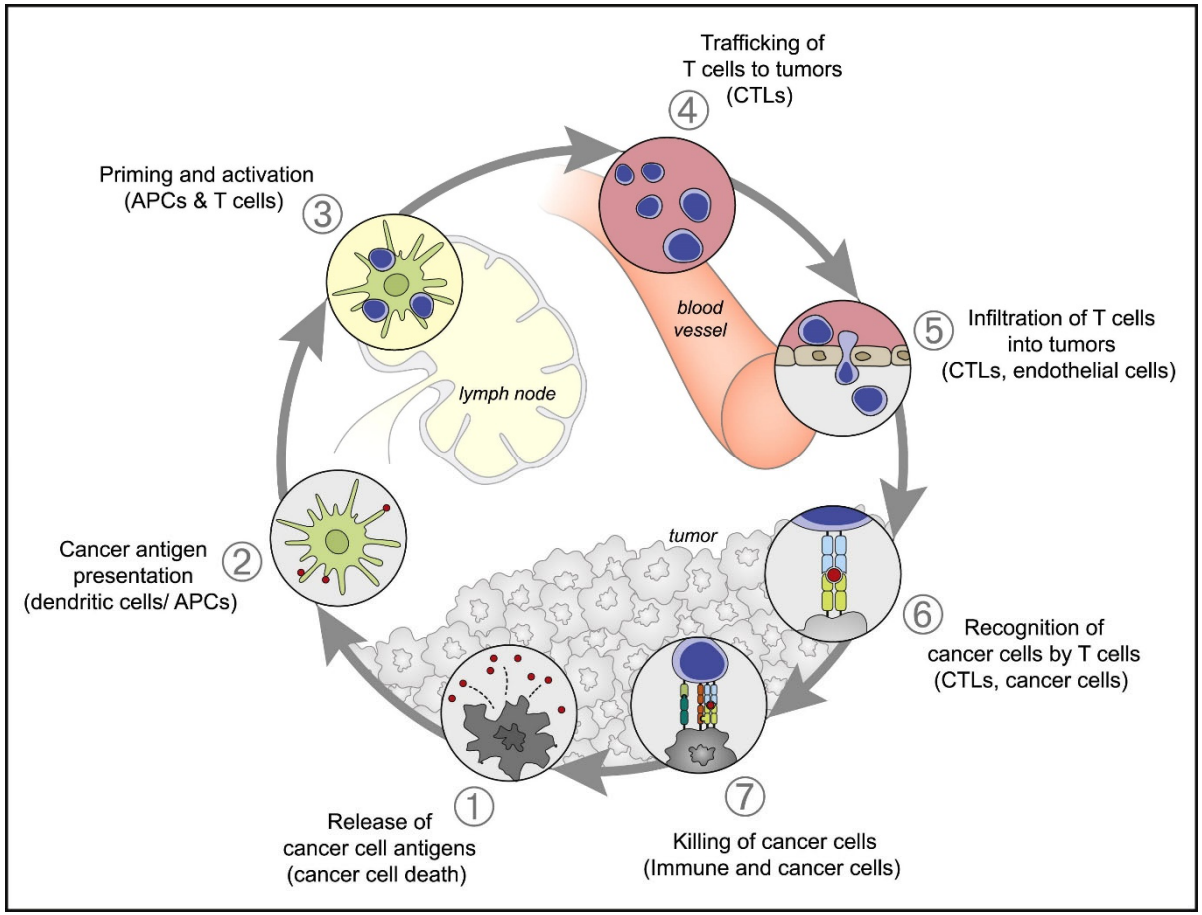
Many diseases associated with the sensors and transducers

- Ataxia Telangiectasia – mutations in ATM
  - Patients are radiosensitive
  - Elevated risk of cancer
  - Have several developmental and neural abnormalities
- AT like disorder – mutations in MRE11
- Nijmegen breakage syndrome – mutations in NBS
- Familial (inherited) breast cancer - BRCA1, BRCA2
  - Inherited breast and ovarian cancer
- Fanconi's Anemia – FANCA,B,C,D1,D2,E
  - FANCB,D1=BRCA2
  - Sensitive to crosslinking agents
  - Increased risk of cancer

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

B

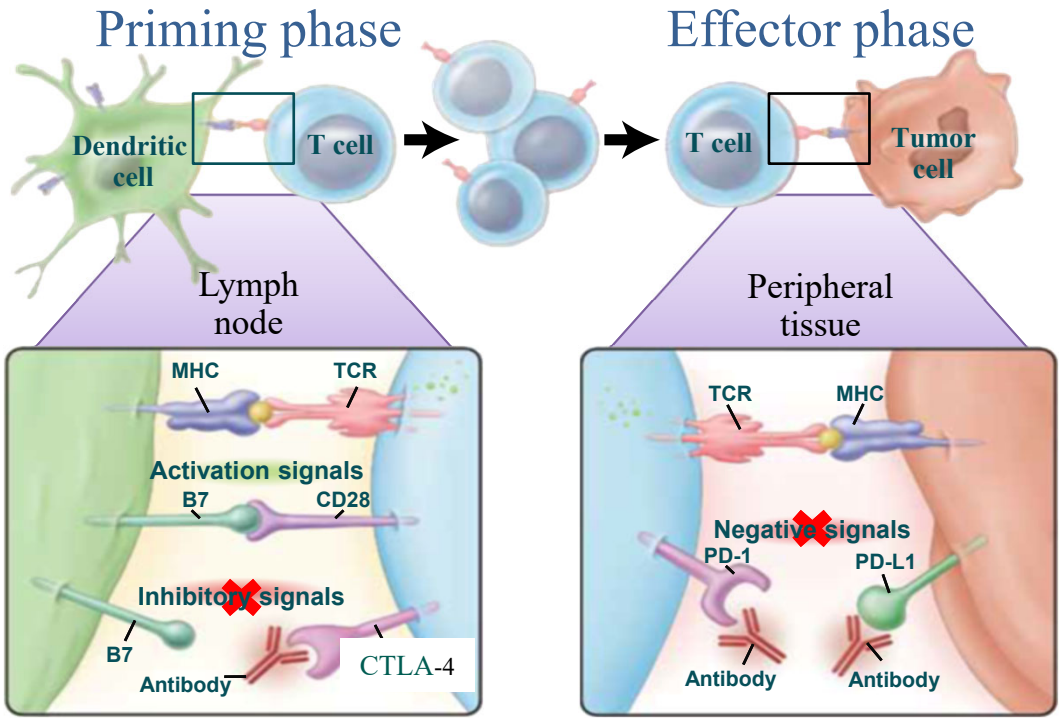
Immune modulation



Chen & Mellman, Immunity, 2013

B

The role of immune checkpoint pathways in the immune response



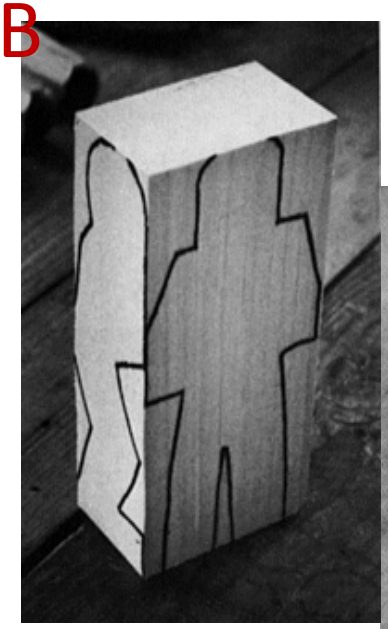
Ribas, NEJM, 2012

Technological aspects of radiotherapy and their evolution

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

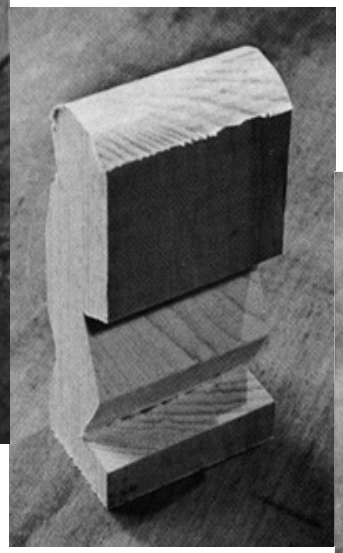
B

Son évolution…



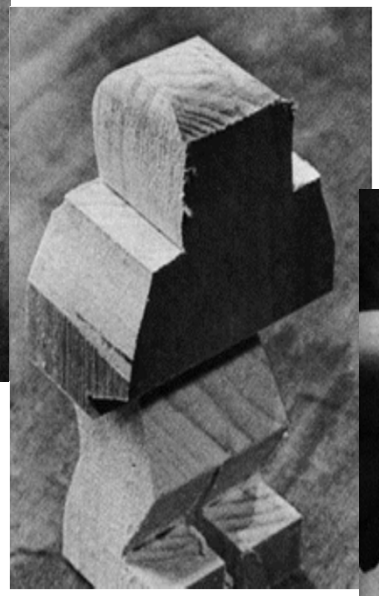
< 1950

2-D Planning



≈ 1960

3-D Conformal



≈ 1990

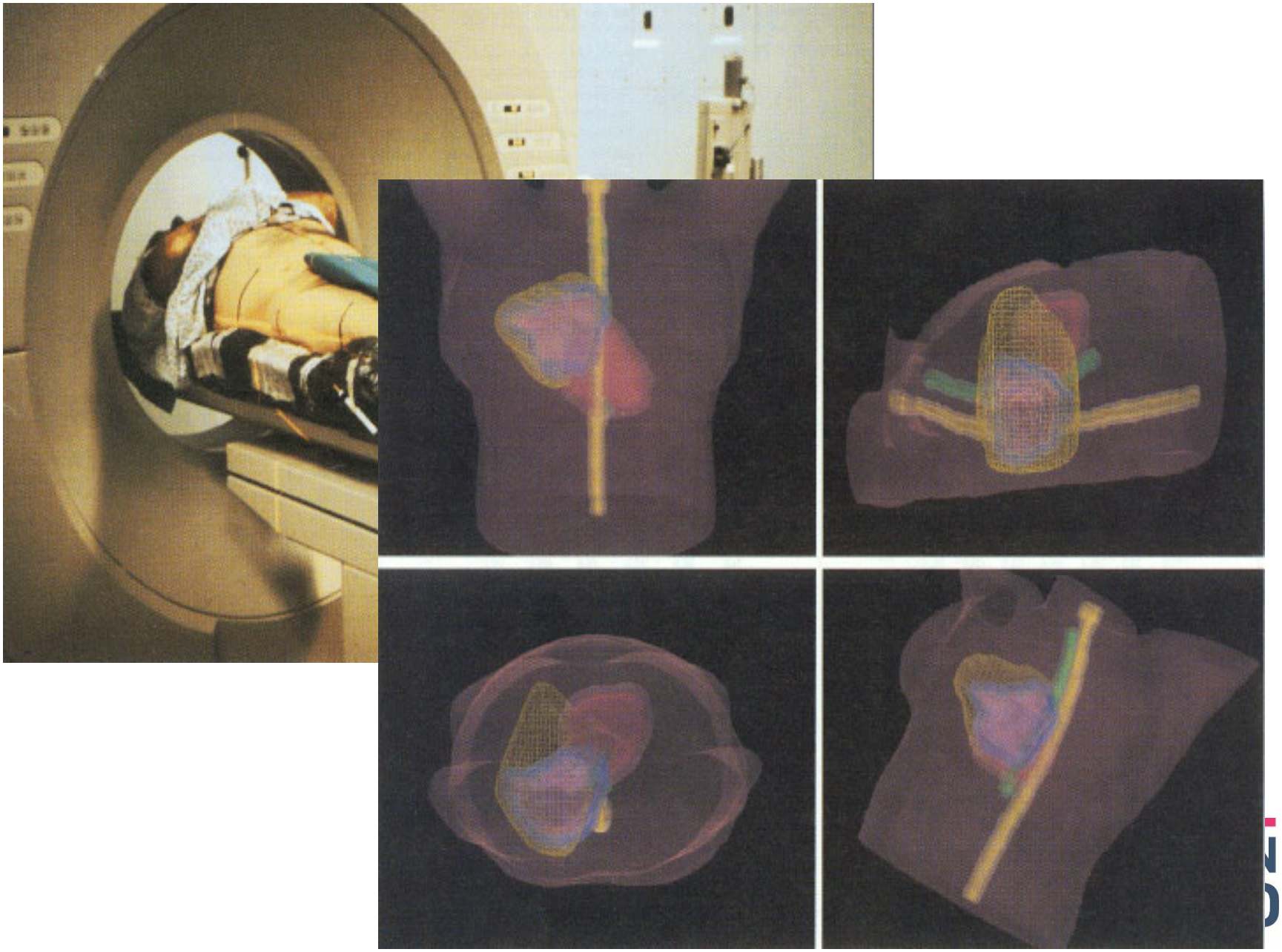
IMRT

≈ 2000

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Courtesy of John Schreiner, Kingston Regional Cancer Centre, Ontario

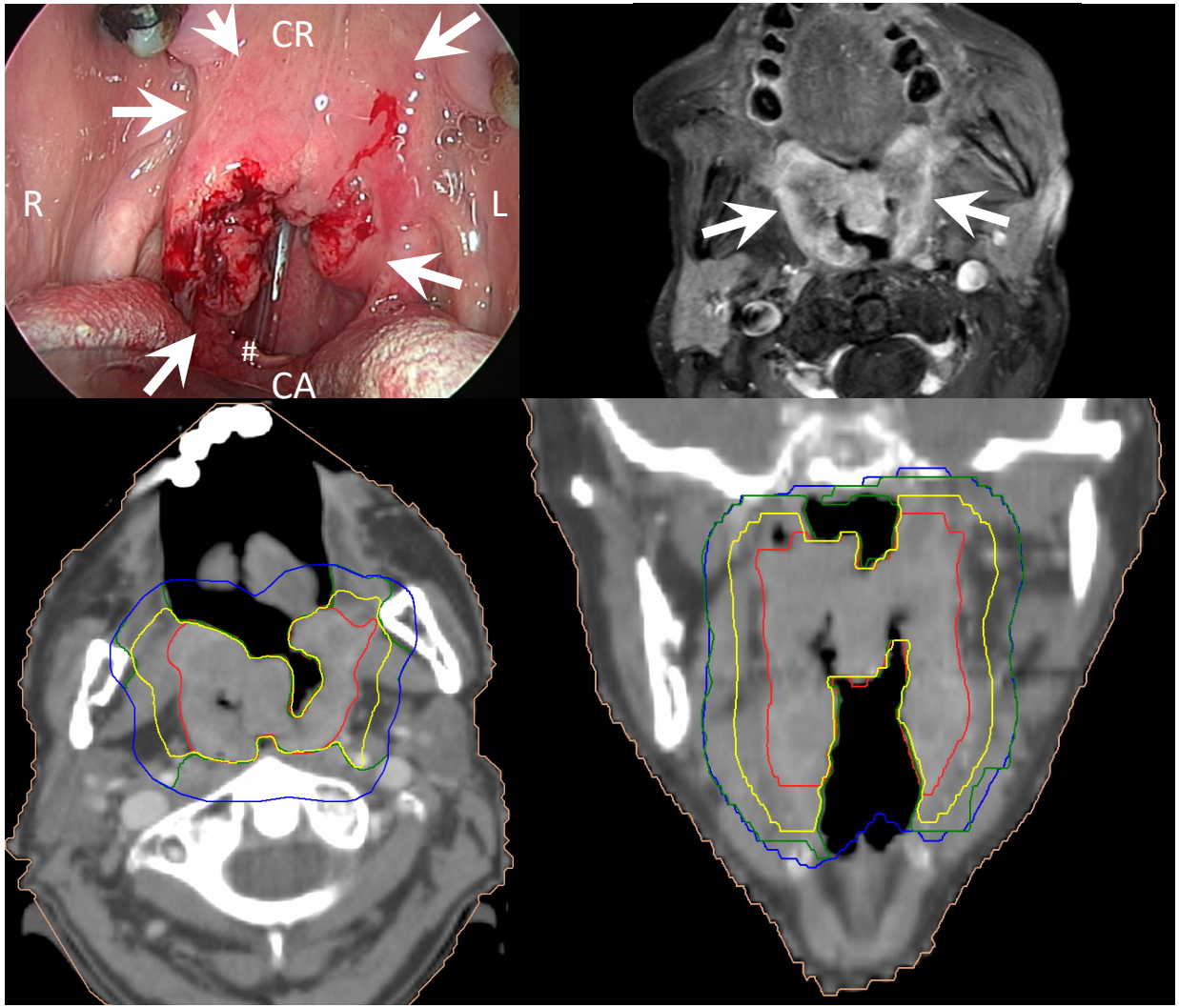
B



C

From GTV_P to CTV_P delineation

T3 soft palate SCC

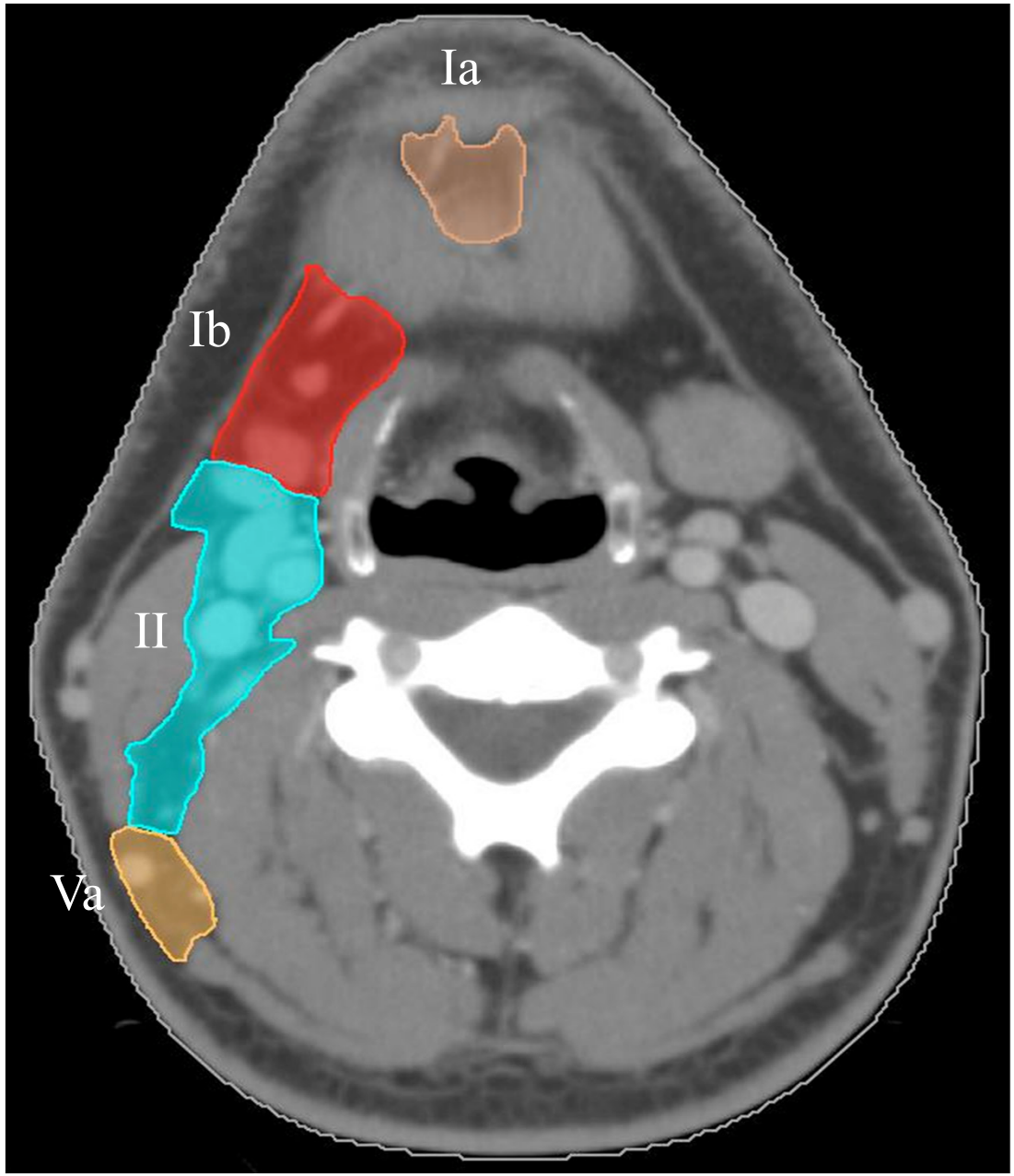


Edited for:

- air cavities
- mobile tongue
- mandible
- vertebral body
- longus colli & longus capiti m.
- epiglottis
- hyoid bone

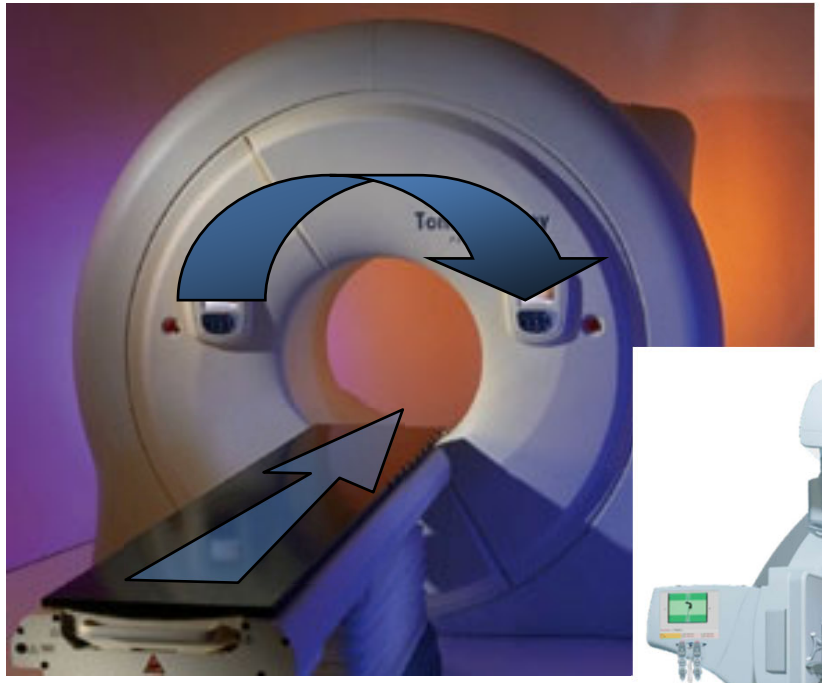
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

C



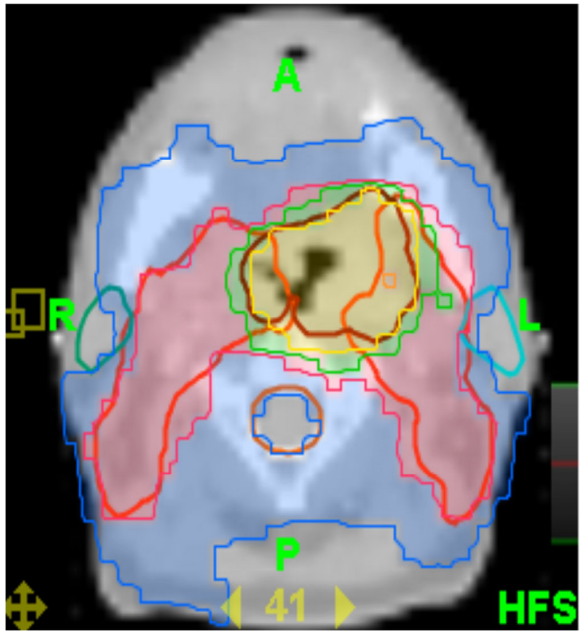
B

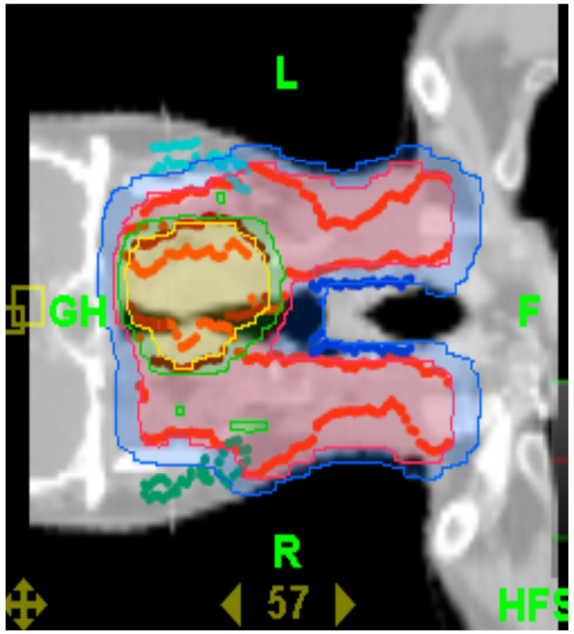
Différents appareils produisant des rayons-X

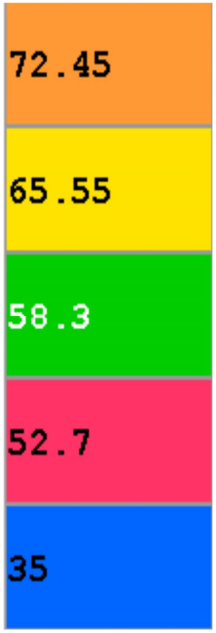


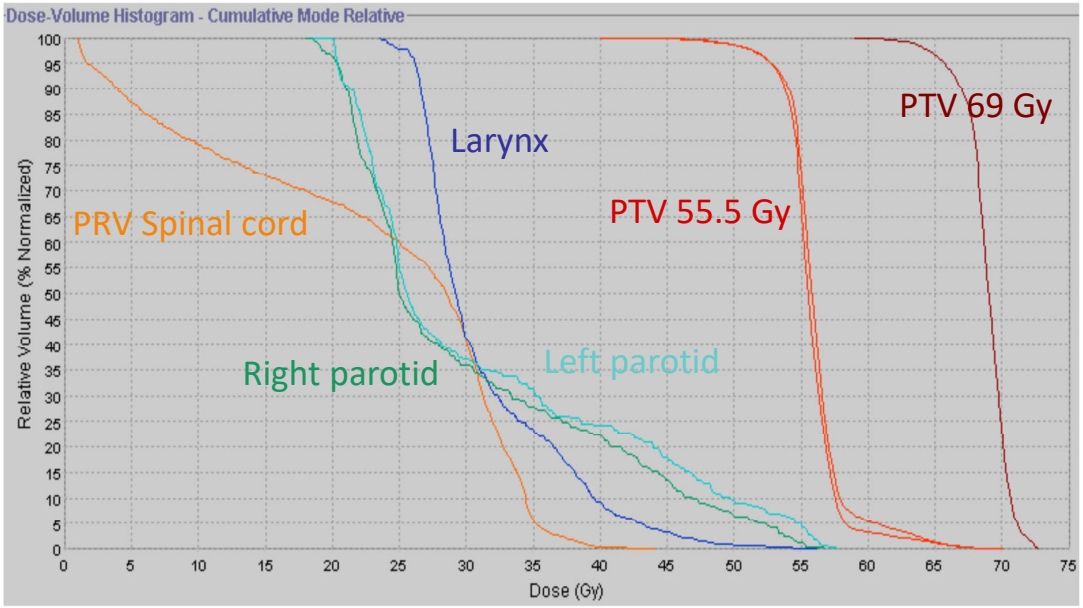
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

AIMRT/VMAT dans les tumeurs Tête & Cou









Oropharyngeal SCC

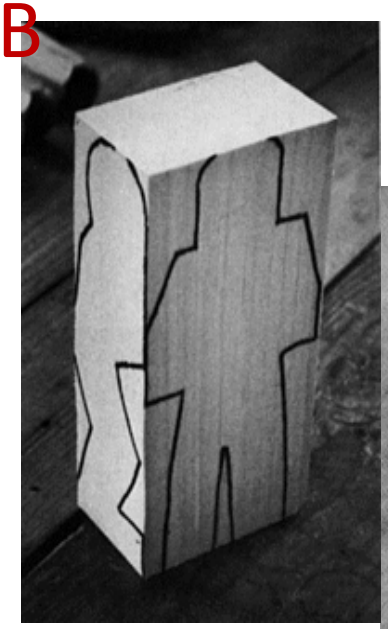
T2-N0-M0

SIB-IMRT: 30x2.3 Gy

30x1.85 Gy

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Son évolution…



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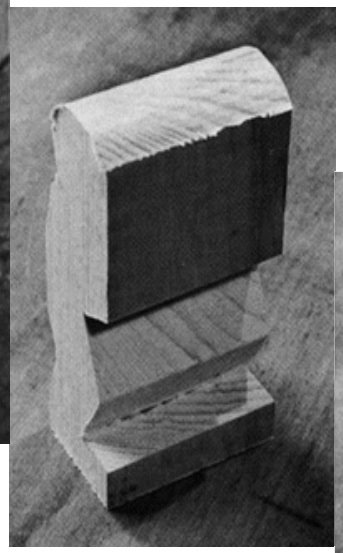

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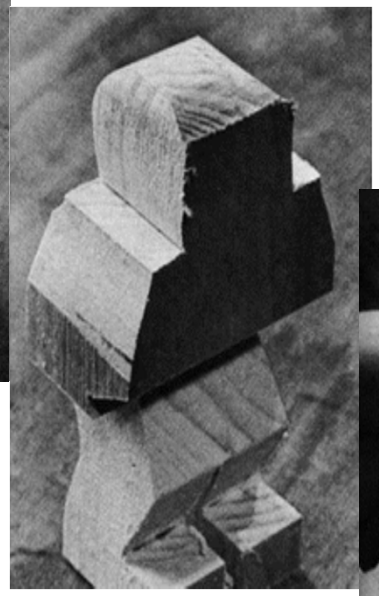


≈ 1990

IMRT

≈ 2000

Dose Painting

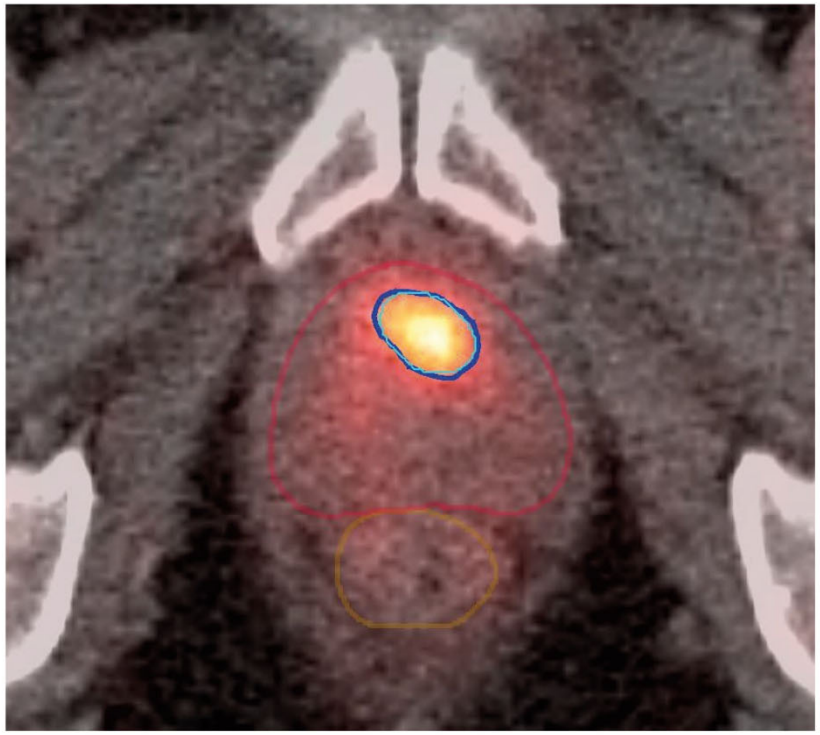
> 2014

Courtesy of John Schreiner, Kingston Regional Cancer Centre, Ontario

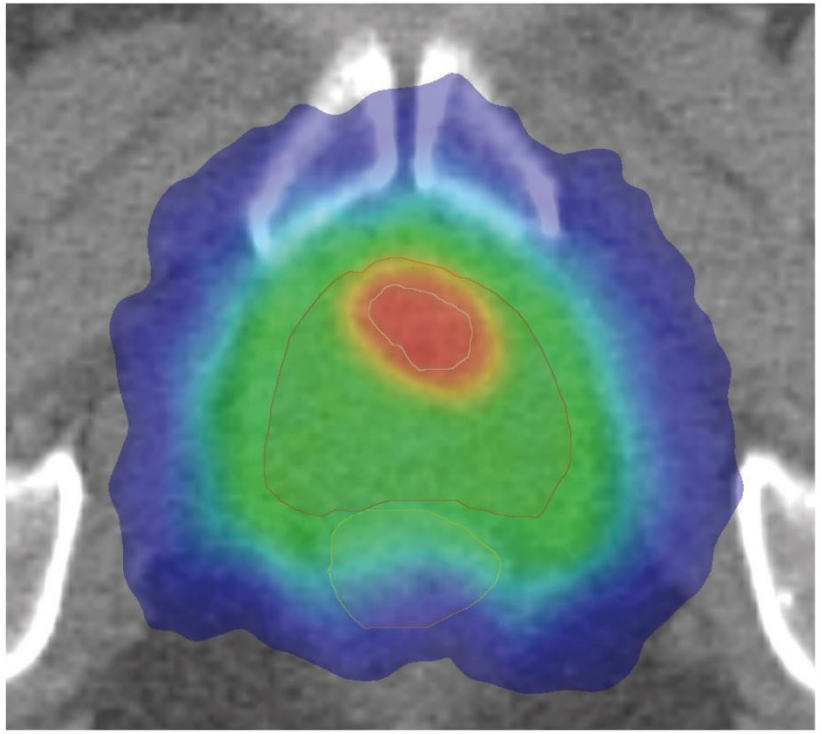
B

IMRT/VMAT dans les tumeurs prostatiques (PET-PSMA)

a)



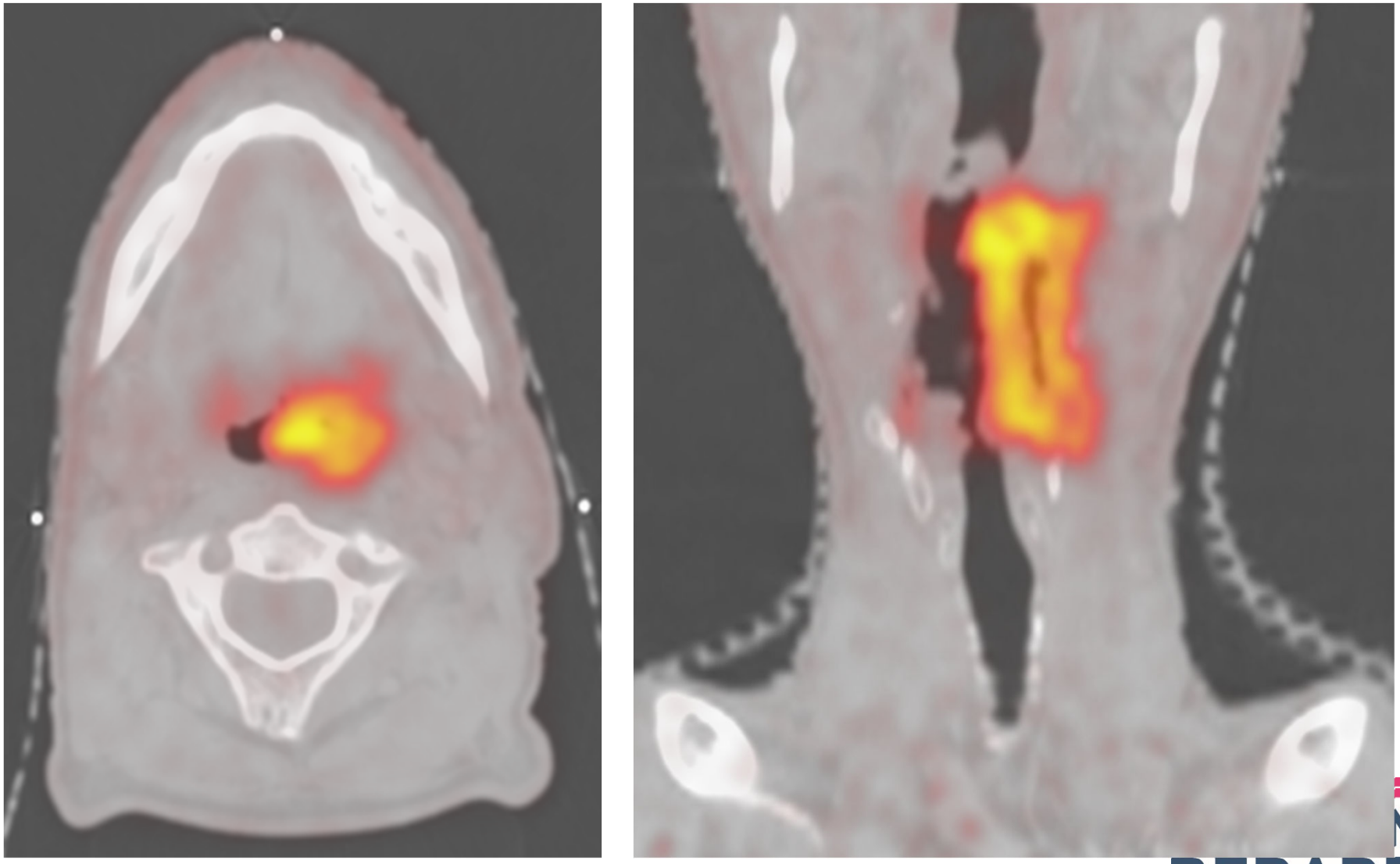
b)



CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

B

Hétérogénéité tumorale (FDG-PET)

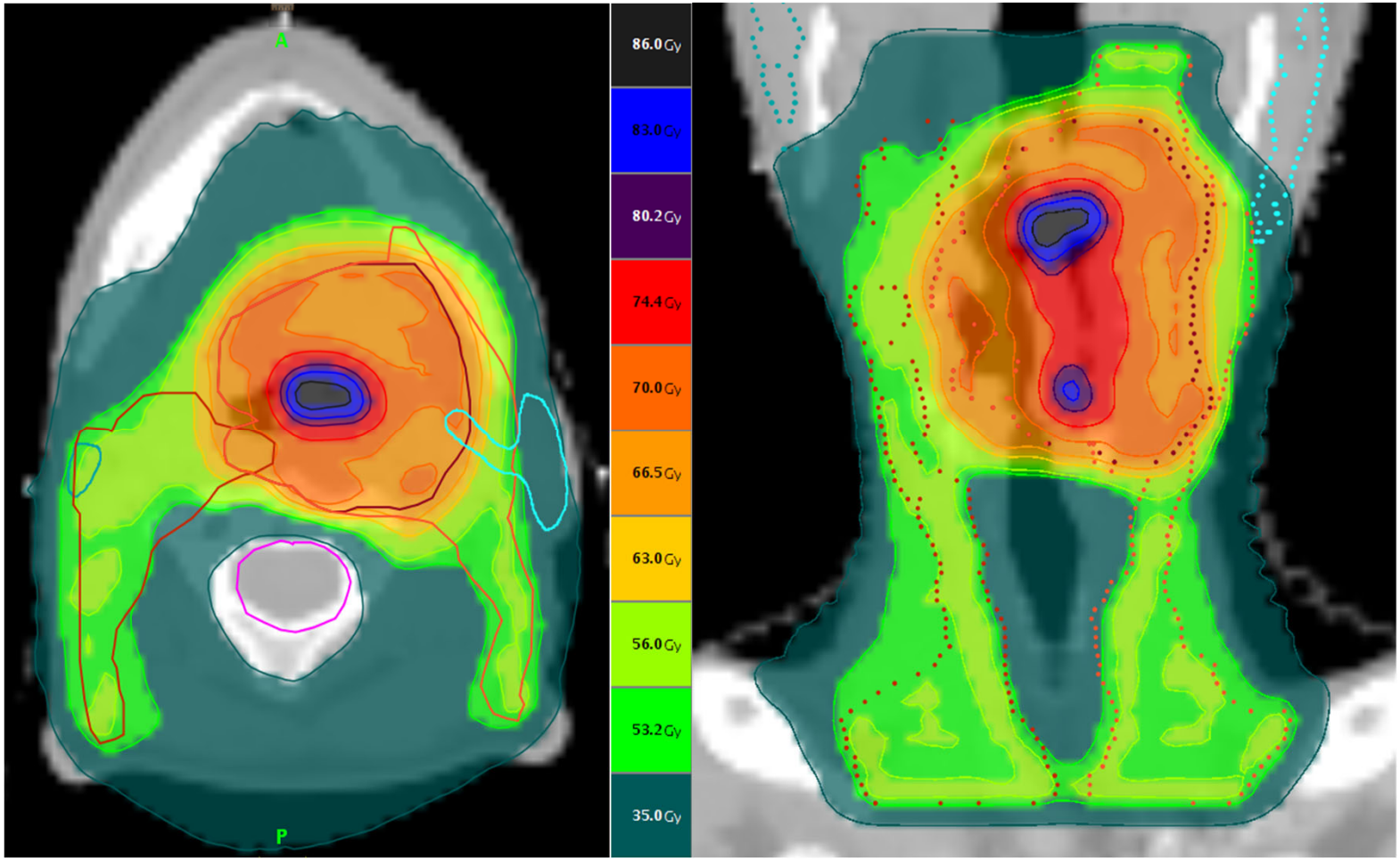


Oropharynx: T4b-N0-M0 – FDG-PET-CT

S. Differding, 2012

B

Dose-painting



Oropharynx: T4b-N0-M0 – FDG-PET-CT

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

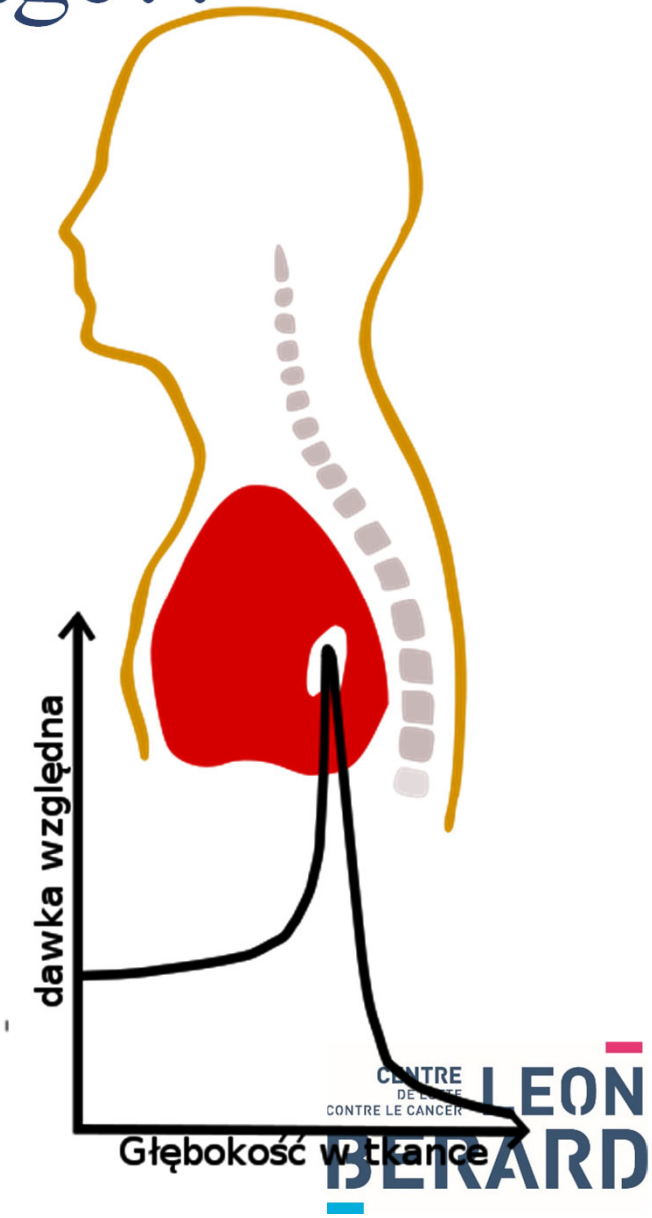
S. Differding, 2012

La protonthérapie…?

A

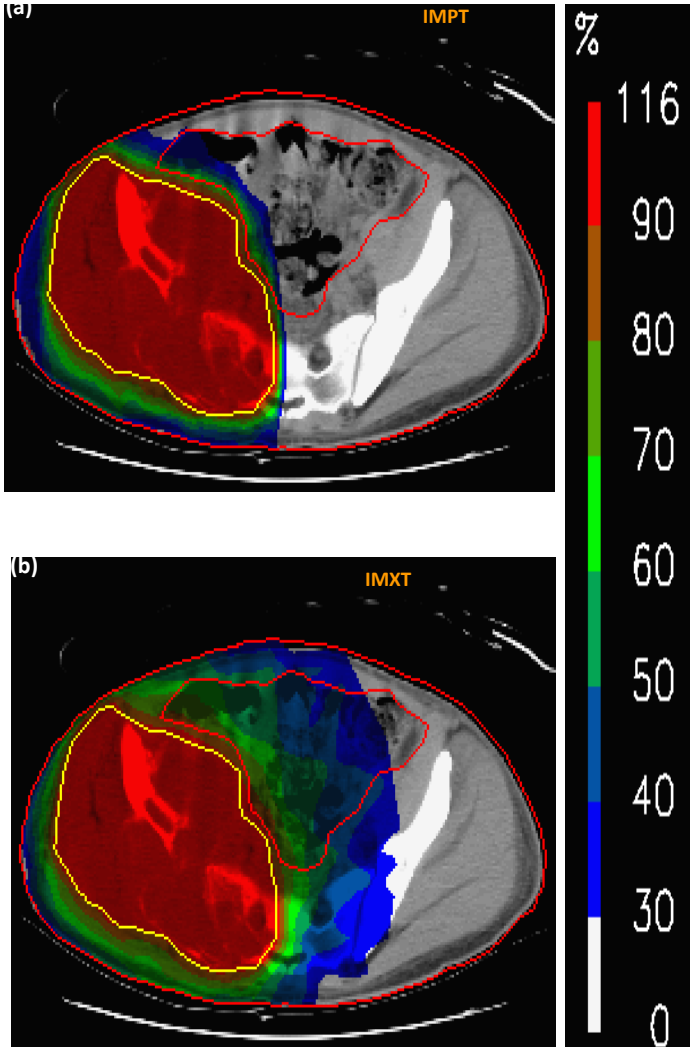
Quel est l'avantage??

- La masse des protons est bien plus grande que celle des électrons
  - Moins de diffusion latérale (donc moins de dispersion)
- Le trajet est limité par l'énergie
  - Et donc la dose est localisée à la profondeur voulue.
- La dose est très élevée en fin de trajet (pic de Bragg).



B

IMRT et IMPT pour un sarcome d'Ewing



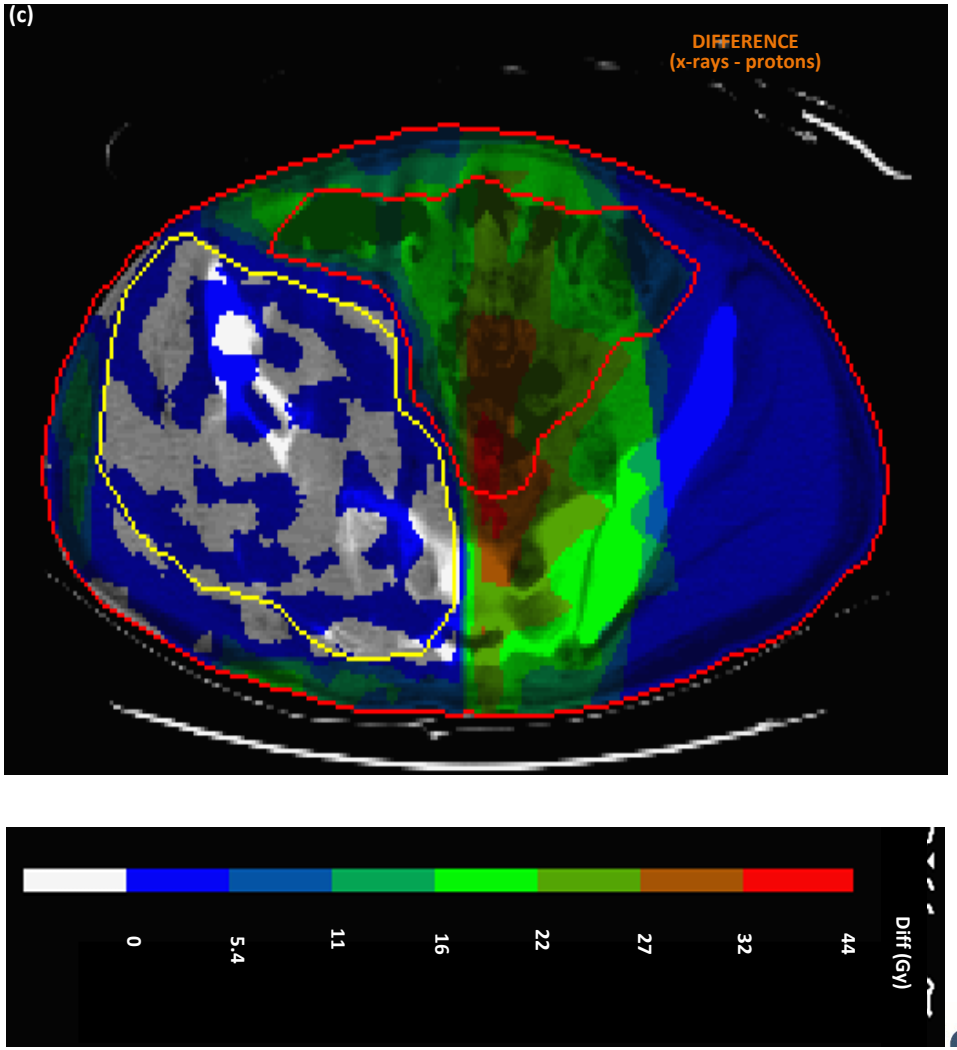
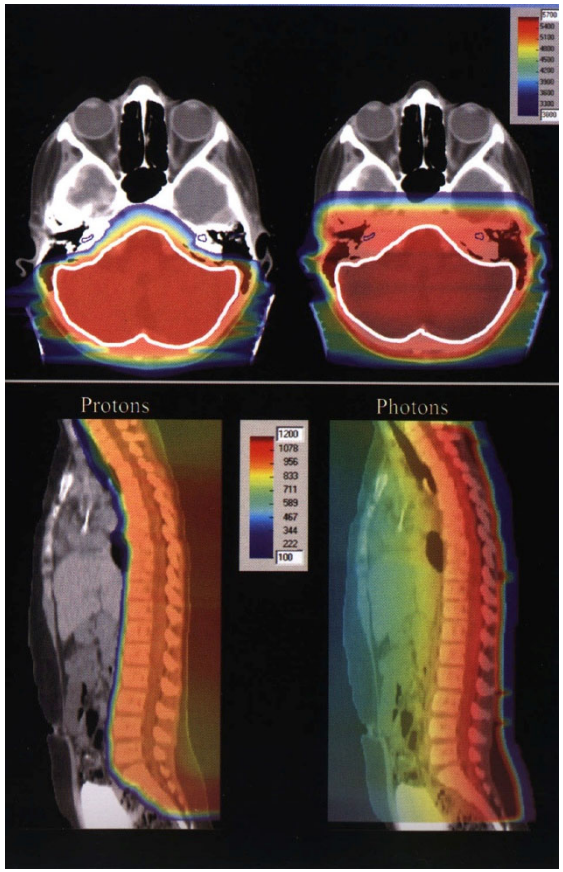


Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

B

Indication principale: pédiatrie

	2000	*2001*	*2003*
leukemia	85	108	90
lymphoma	39	43	34
Embryonal tumours	52	54	63
CNS	94	68	65
Bone	15	18	24
STS	35	34	35
total	**320**	**325**	**313**



Medulloblastome chez un enfant de 5 ans
4 MV photons vs. protons

Recrutement potentiel en France de ± 600 cas/ selon les pratiques actuelles

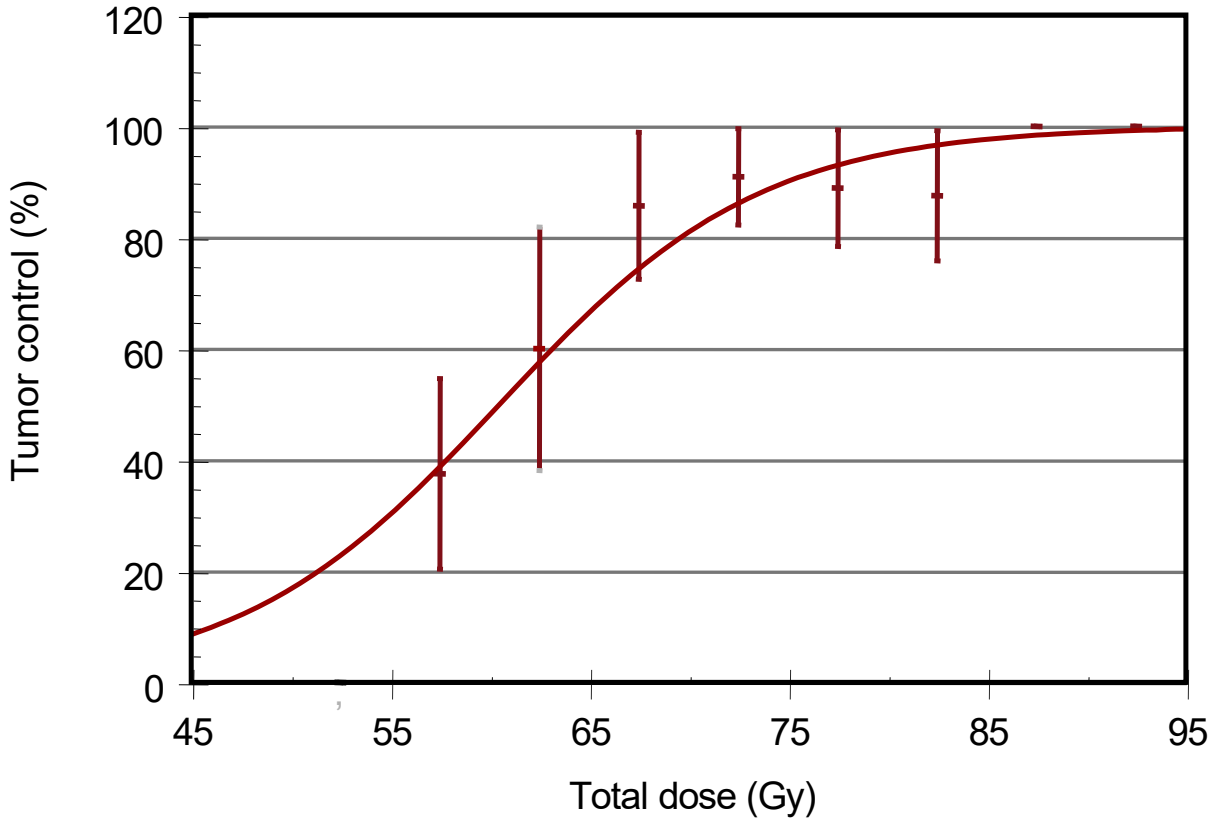
CENTRE DE LUTTE E LE CANCER LEON BERARD

Clinical considerations: efficacy and toxicity of radiotherapy

A

Tumor Control Probability (TCP)

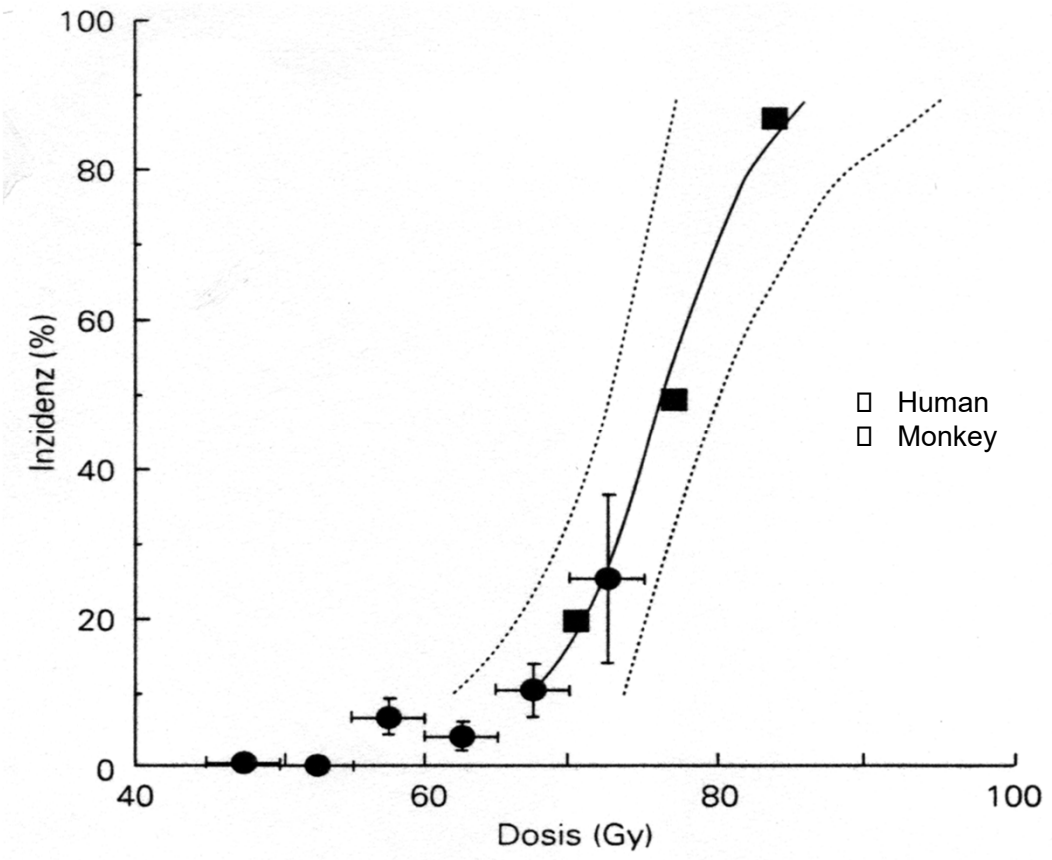
Dose-response curve for neck nodes ≤ 3 cm



Bataini et al, 1982

A

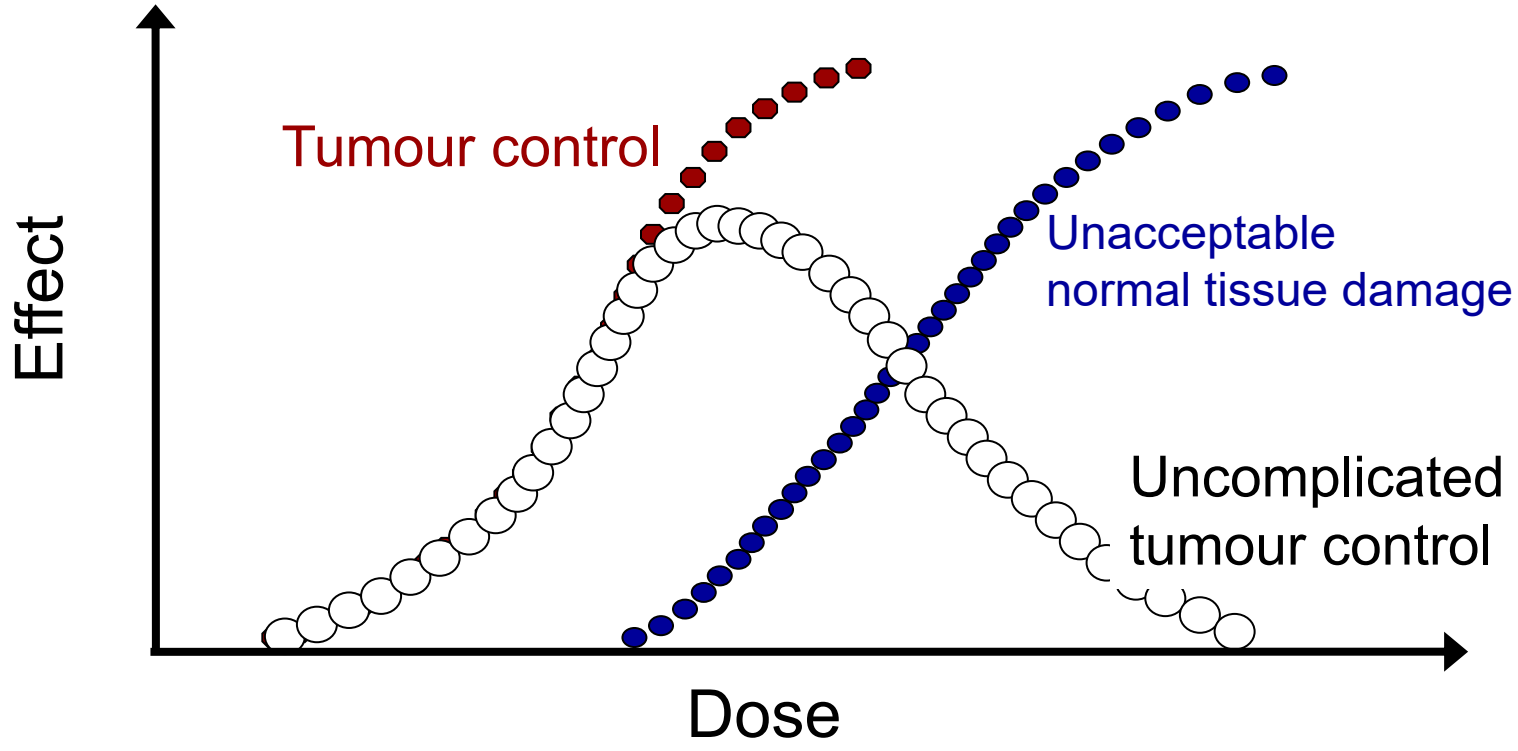
Normal Tissue Control Probability (NTCP)



Baumann et al., Strahlenther Onkol 170: 131-139, 1994

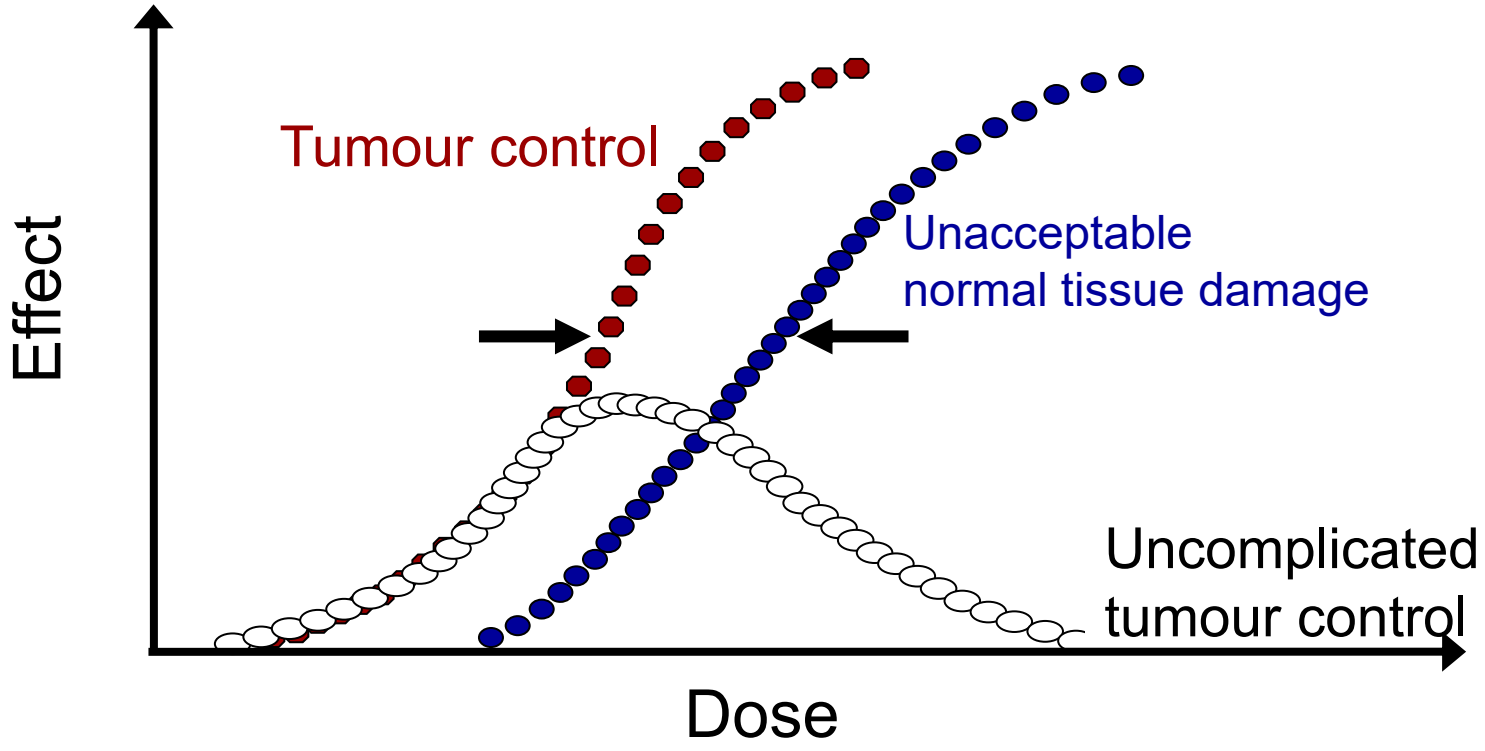
A

Uncomplicated tumor control: Therapeutic Ratio



B

Uncomplicated tumor control: Therapeutic Ratio



CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

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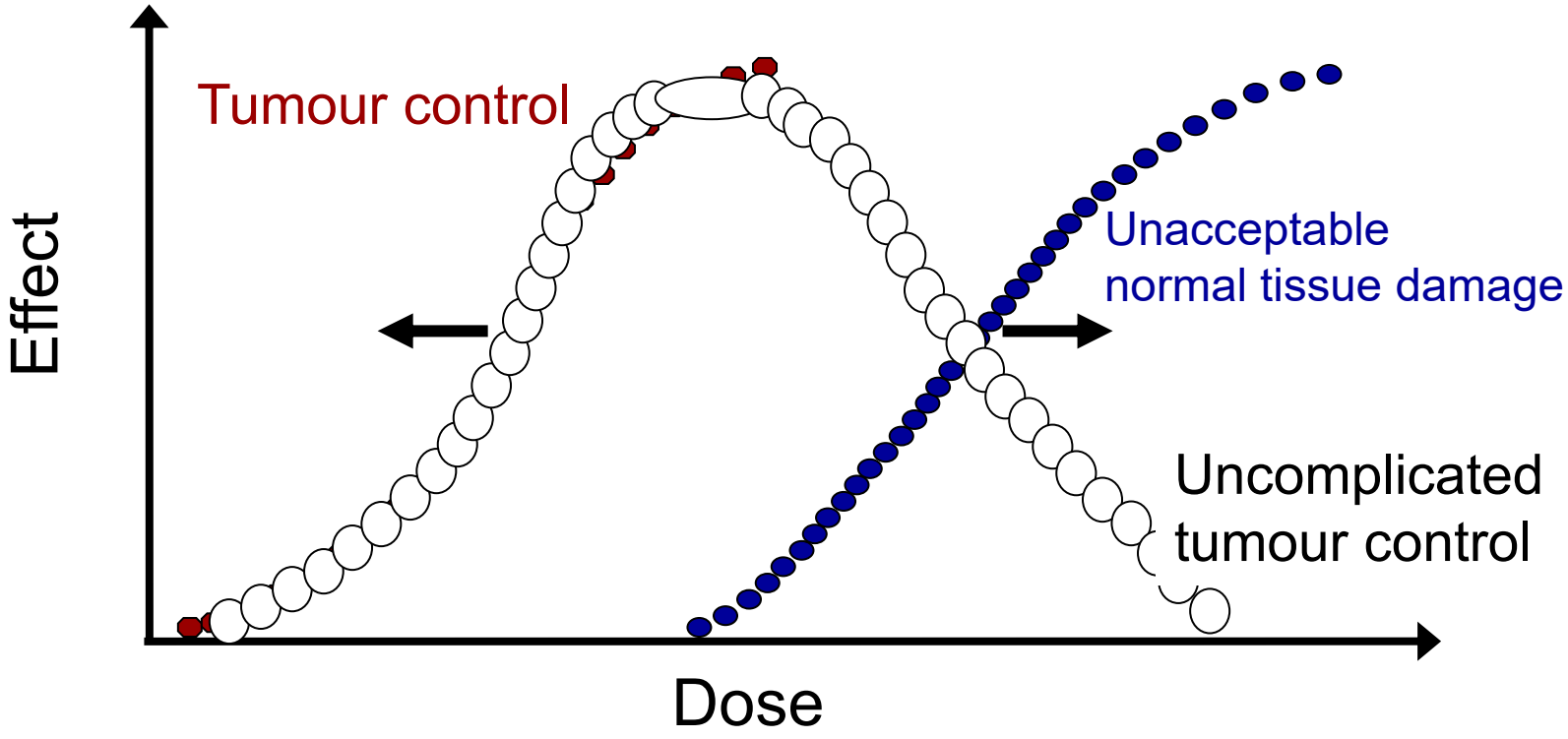
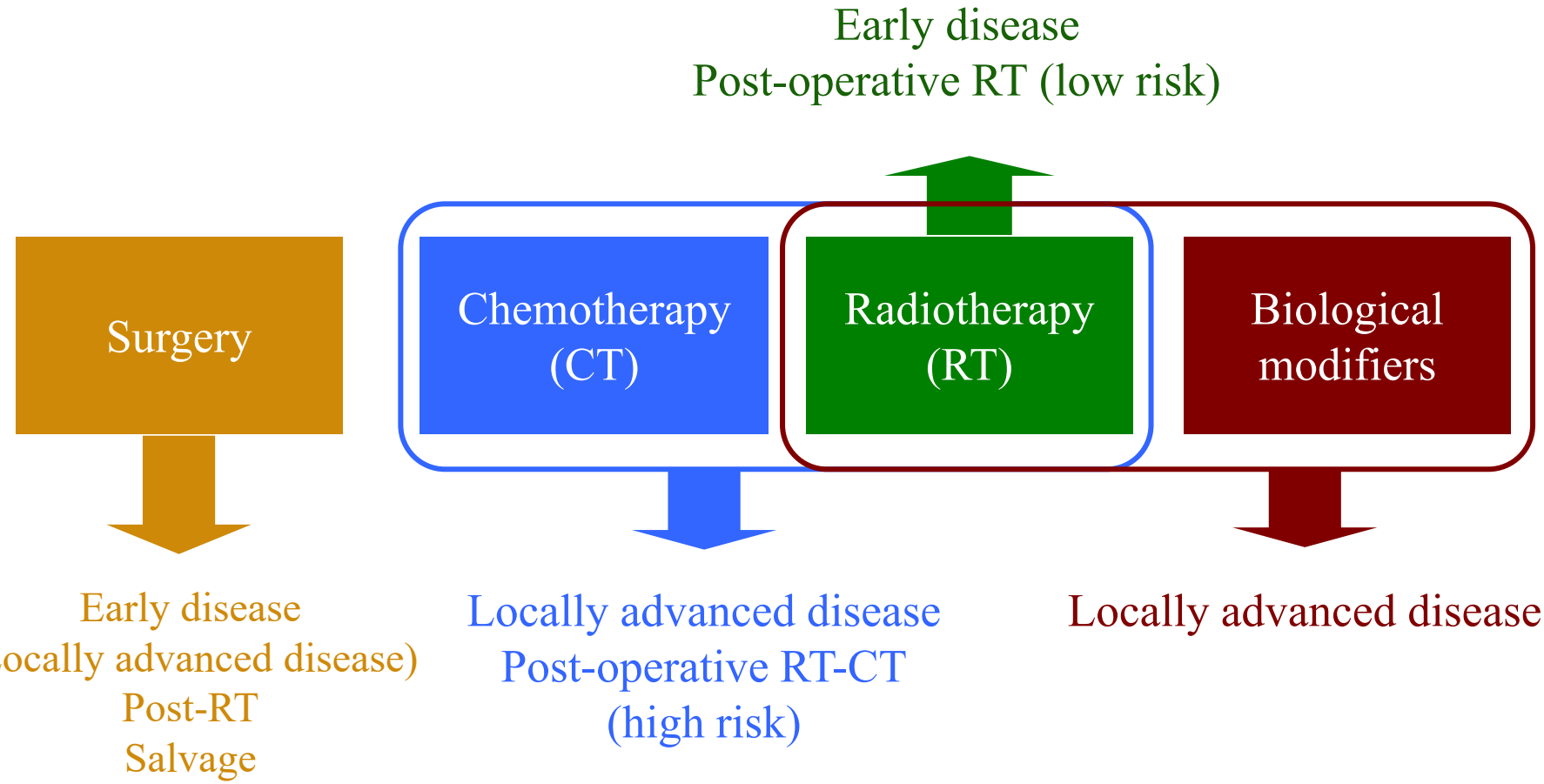
Uncomplicated tumor control: Therapeutic Ratio



A Radiotherapy in the armomentarium of cancer treatment



A

Conventional fractionation

1.8 – 2.0 Gy per fraction, 5 fractions per week

IIIII IIIII IIIII IIIII IIIII IIIII IIIII

	Example	Dose (Gy)	Tumor control (%)
Sensitive	Seminoma, Lymphoma	≤ 45	≥ 90
Intermediate	SCC, Adeno-Ca	50	≥ 90 (subclinical)
		60	~ 85 (Ø 1 cm)
		70	~ 70 (Ø 3 cm)
			~ 30 (Ø 5 cm)
Resistant	Glioblastoma	≥ 60	none?
	Melanoma	≥ 60	none?

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

Indications

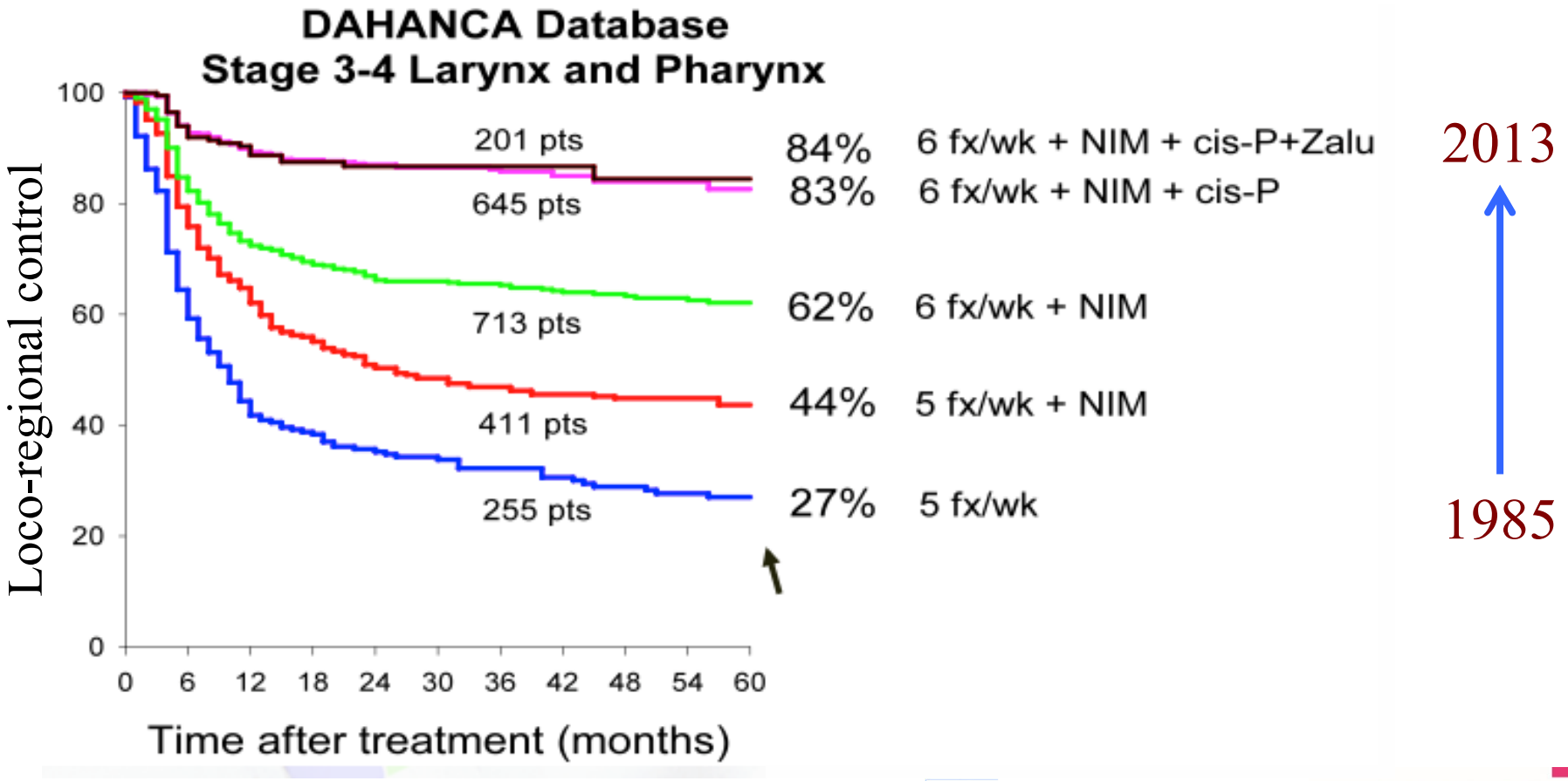
Traitements curatifs loco-régionaux de première intention ± chimiothérapie / biological modifiers

- T cérébrales, ORL, oesophagiennes, pulmonaires, prostatiques, hématologiques, digestives, cutanées, testiculaires, gynecologiques, …
- Patients non-opérables, e.g. patient âgé, avec co-morbidité, …
- Tumeurs non-résécables (e.g. localement avancées)
- “organ preservation strategy” (par ex. T du larynx, T de la marge anale)

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

B

The DAHANCA strategy:
progression through consecutive clinical trials



DAHANCA.dk

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Overgaard et al., 2016

A

Indications

Traitements curatifs loco-régionaux adjuvants ± chimiothérapie / biological modifiers

- T cérébrales, ORL, oesophagiennes, pulmonaires, mammaires, prostatiques, hématologiques, digestives, cutanées, testiculaires, gynécologiques, sarcomes, …

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

Indications

Traitements curatifs loco-régionaux neo-adjuvants ± chimiothérapie / biological modifiers

- T du rectum, gynécologiques, sarcomes, …

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

Indications

Traitements palliatifs

- Objectifs: retarder l'évolution fatale et/ou soulager un symptôme
- Exemples: - métastases osseuses douloureuse: e.g. 1 x 8 Gy
  - métastases osseuses unique: RxTh stéréotaxique, e.g. 3 x 10 Gy
  - métastases pulmonaire unique: RxTh stéréotaxique, e.g. 3 x 10 Gy
  - saignement vésical: 1 x 8 Gy
  - métastases cérébrales: irradiation pan-cranniène ou stéréotaxique

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Prototypes of modified fractionation regimens

- Normo-fractionnation

70Gy/ 2.0 Gy/ 7w

- Hyperfractionation (e.g. H&N)

80.5Gy/ 2x1.15 Gy/ ti=6h/ 7w

- Accelerated fractionation (e.g. H&N)

70Gy/ 2.0 Gy/ 5w

- Hypofractionation (e.g. breast, prostate, paliation)

67.5 Gy/13.5 Gy/ 2w

75Gy/ 2.5 Gy/ 5w

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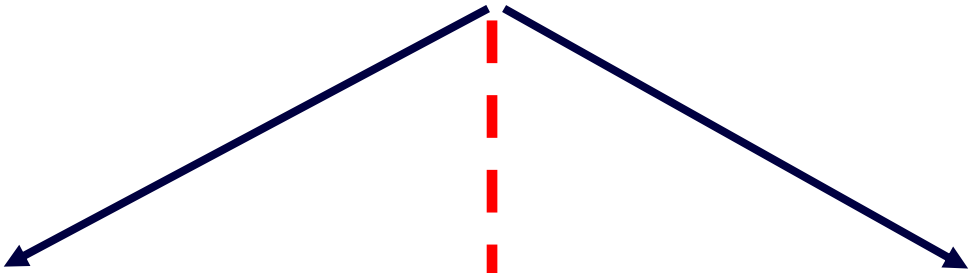
B

Radiotherapy side effects



Early (acute) reactions

bone marrow
oral mucosa
intestinal mucosa
epidermis
...

90 days

Late (chronic) responses

lung
CNS
kidney
dermis
...
...

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

Toxicité aiguë de la radiothérapie

- Cutanée
  - Erythème (15-20 Gy)
  - Epithélite exsudative

    R/ pommade calendula, éosine aqueuse
- Muqueuse
  - ORL : mucite, xérostomie, oesophagite, agueusie

    R/ bains de bouche (alcalins +- antifongiques), prophylaxie dentaire, antalgie, alimentation
  - Digestive : ténesme, diarrhées, anite, poussée hémorroidaire, rectite

    R/ locaux, anti-diarrhéiques

  - Vésicale & uréthrale : cystite radique

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

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Toxicité aiguë de la radiothérapie

- Hématologique : si volume important de moelle osseuse irradiée (e.g. bassin + rachis)
  - Anémie, lymphopénie, thrombopénie

    R/ transfusion, ⚠⚠⚠ facteurs de croissance, …
- Digestive
  - Vomissements, nausées

    R/neuroleptiques, sétrons si besoin
- Pulmonaire : pneumopathie radique aigue

    R/ corticoides
- Neurologique : HTIC si RTE cérébrale

    R/ corticoides, mannitol, …

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

A

Toxicité tardive de la RTE : fibrose

- Cutanées : pigmentation modifiée, fibrose, (alopécie rarement définitive)
- Cardiaque : insuffisance cardiaque, péricardite, ischémie coronarienne
- Digestives : sténose post-radique (œsophage), grêle radique, recto-colite radique
- Urologique : vessie radique, sténose urétérale (rare)
- ORL : xérostomie, ostéoradionécrose, séquelles trophiques

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Toxicité tardive de la RTE

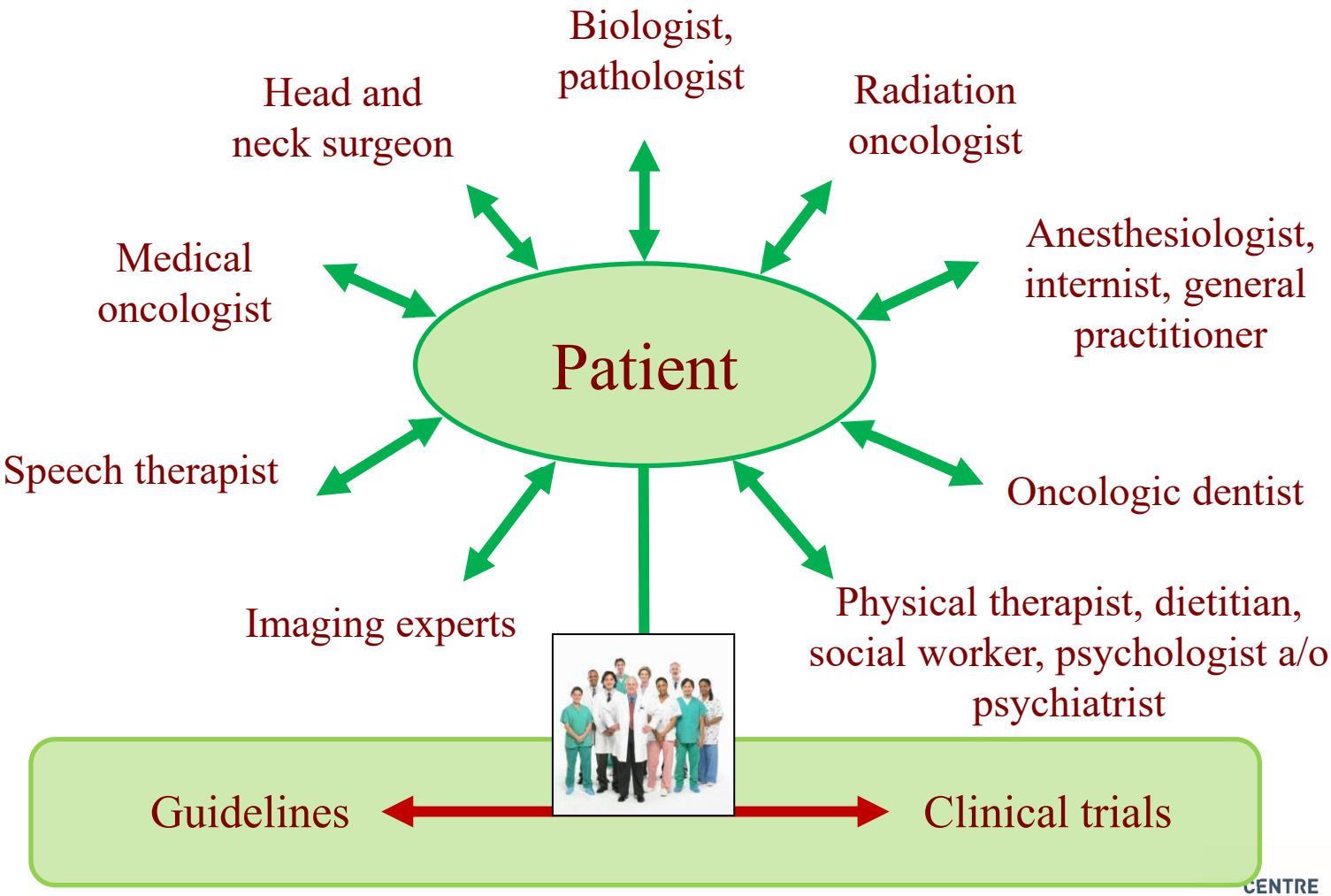
- Neurologique
  - cérébrales : encéphalopathie radique, radionécrose cérébrale
  - myelopathie radique : obsession +++
  - plexite radique
- Troubles de croissance
- Troubles endocriniens
  - Hypophyse : panhypopithuitarisme
  - Thyroide : hypothyroidie
  - Gonades : stérilités
- Cancers radio-induits (<1%)
  - Sarcomes ++
  - 3-30 ans
  - En champ irradié

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

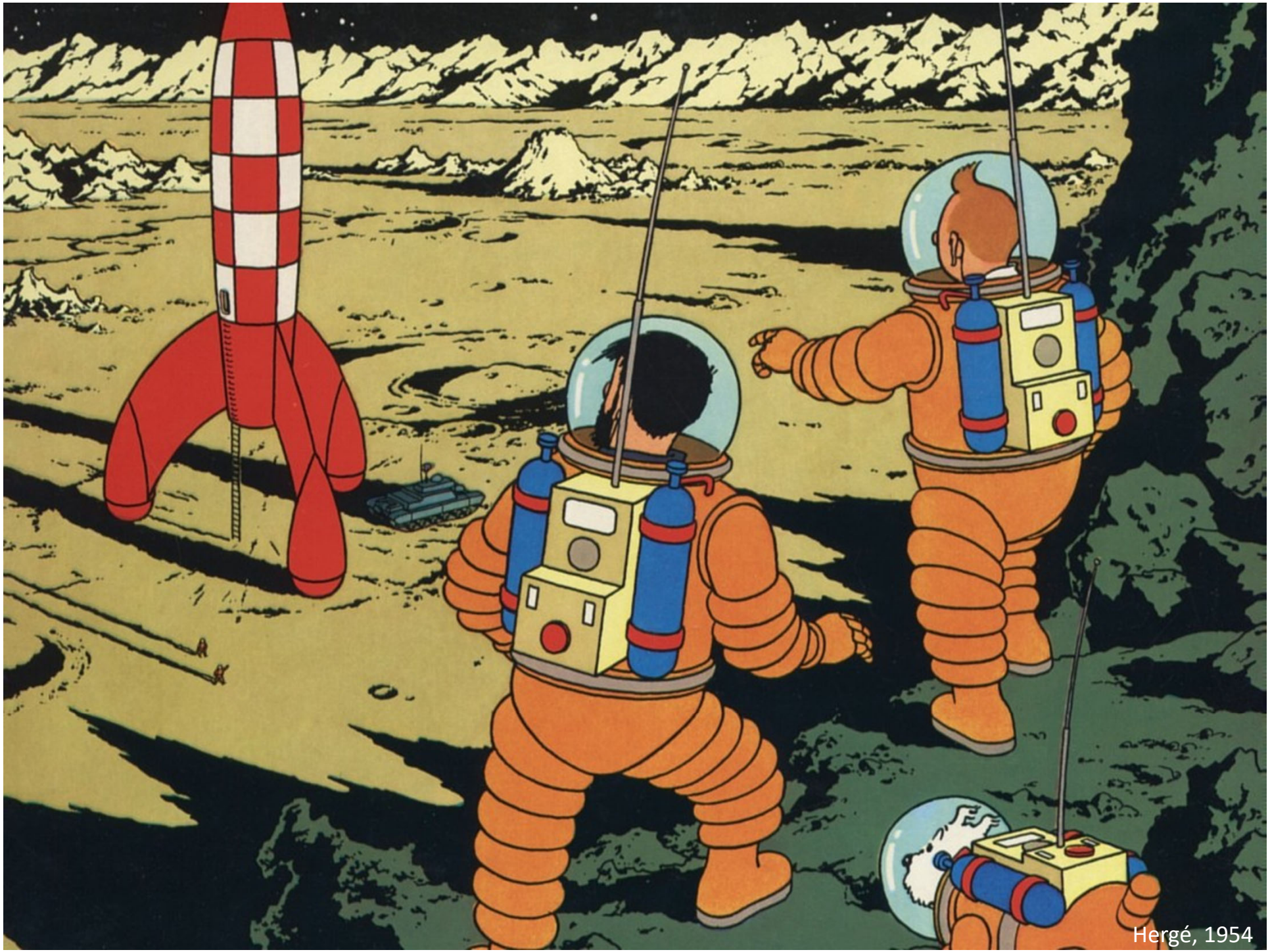
Conclusions

A

Multidisciplinary patient management



Courtesy of J. Vermorken, 2018


Hergé, 1954