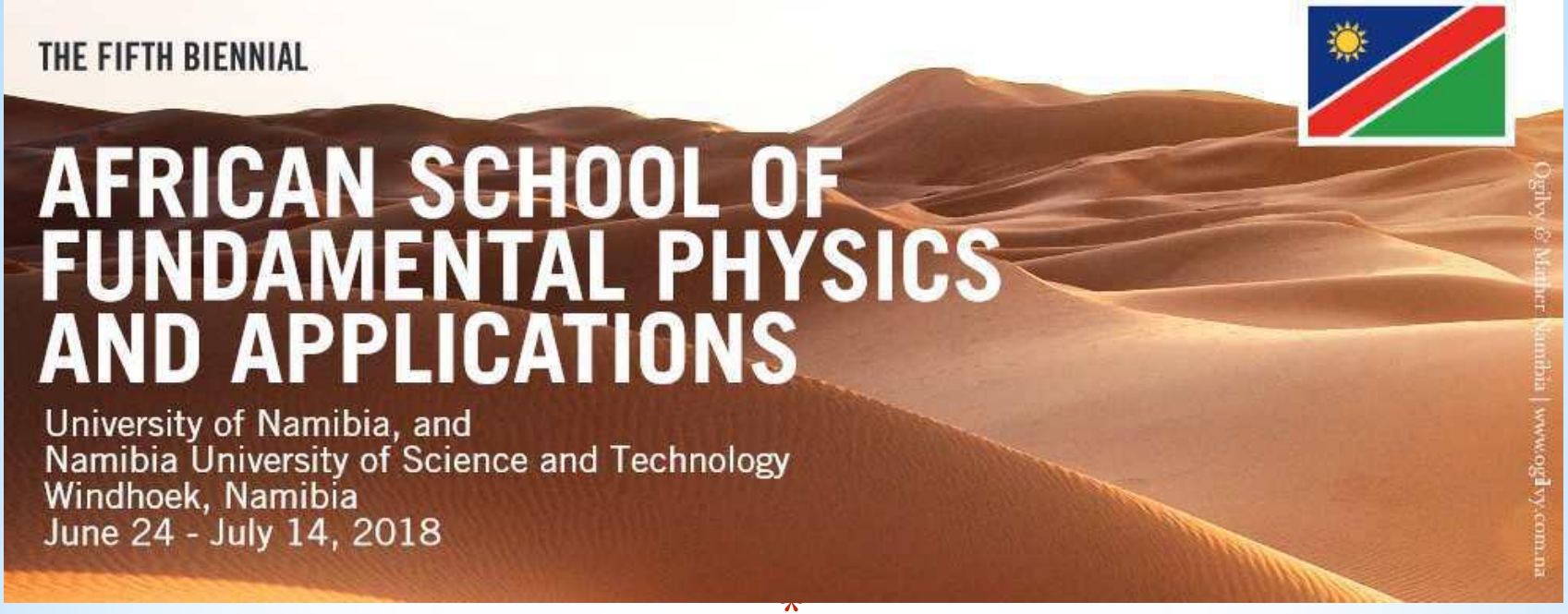

Biological Basis of Clinical particle physics

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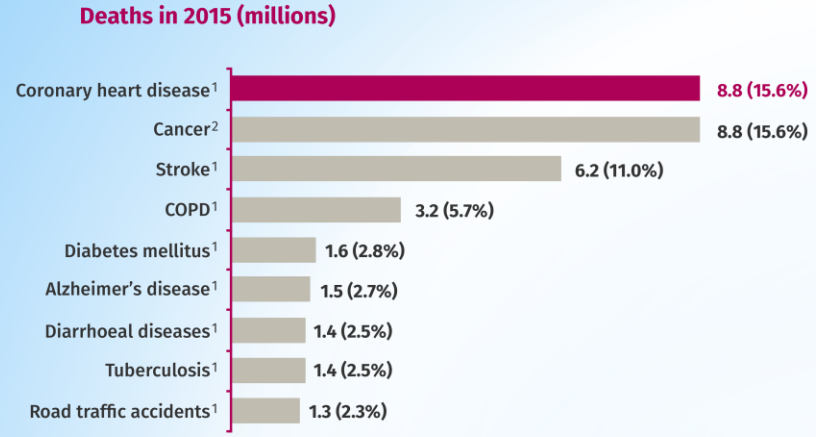
Segal Cancer Centre
Jewish General Hospital
Montreal, Qc, Canada

* I have no disclosure

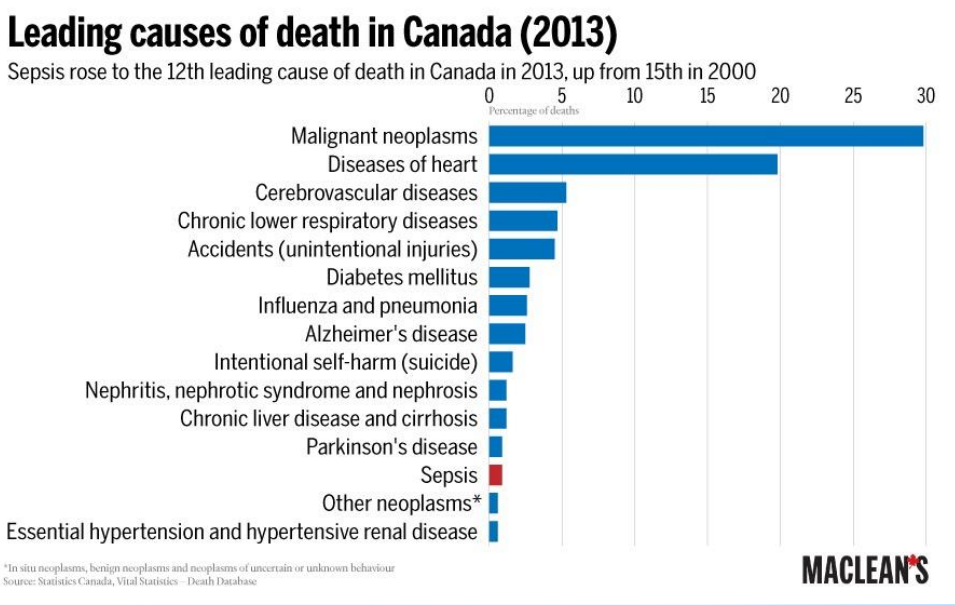
Outline

- Statistics: mortality rates
- Hallmarks of cancer
- Physics & Chemistry of Radiation Absorption
- Radiobiological basis of Radiotherapy
- Treatment Planning
- Charged particles

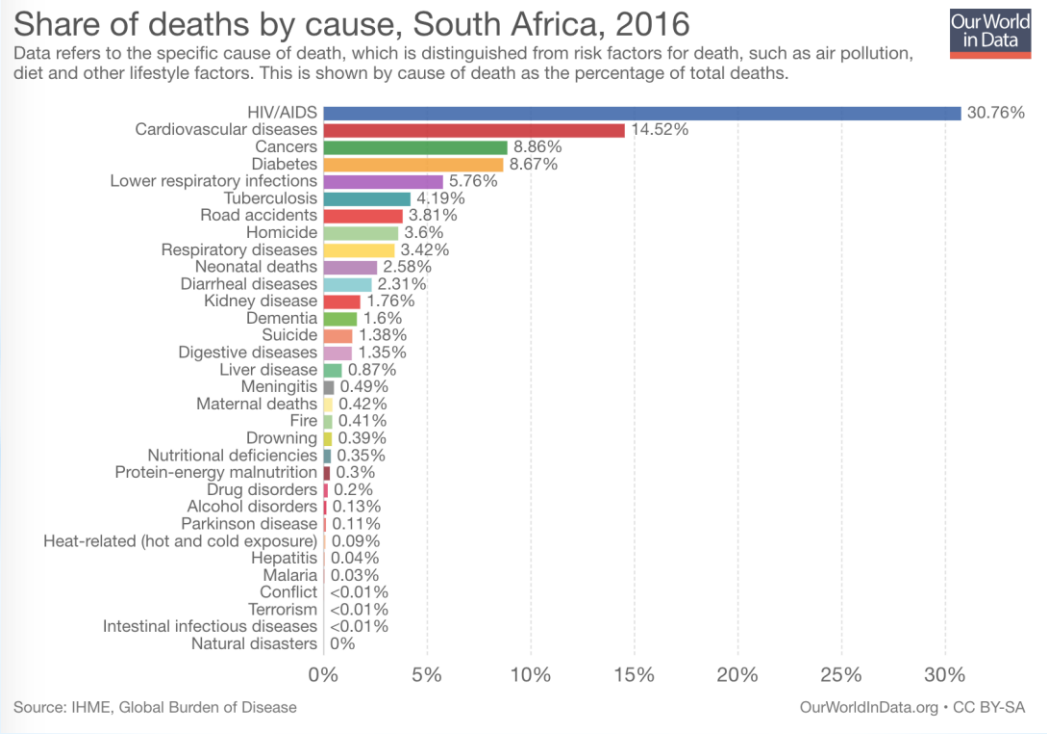


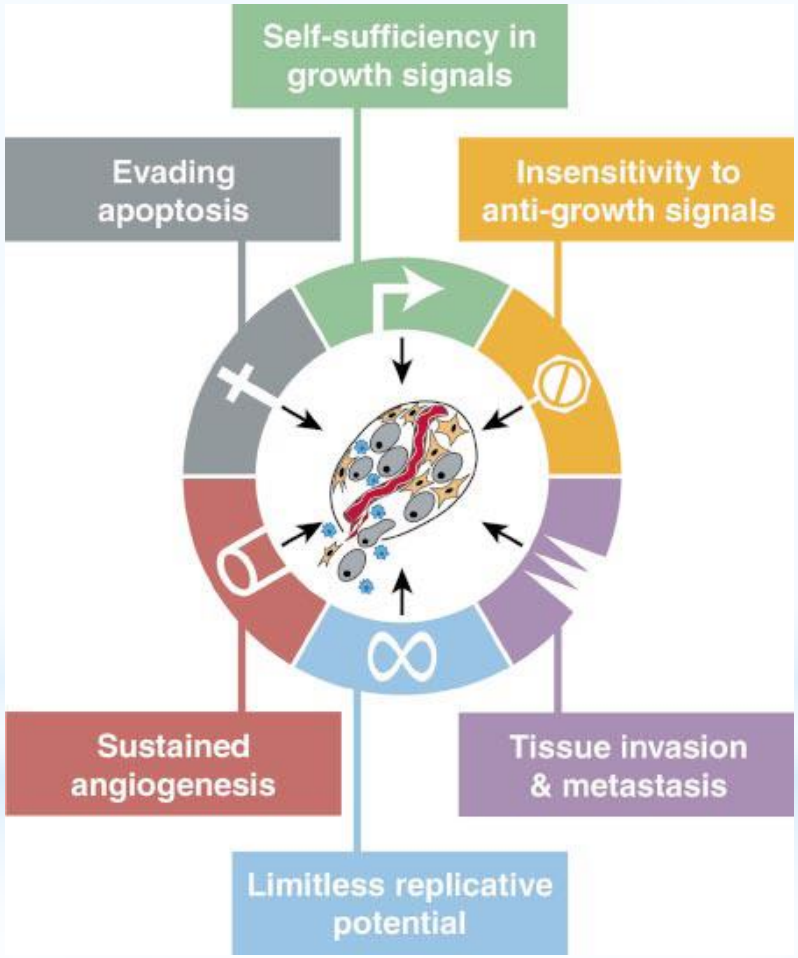
COPD, chronic obstructive pulmonary disease. In 2015 there were 56.4 million deaths worldwide

1. World Health Organization. Fact Sheet No. 310. http://www.who.int/mediacentre/factsheets/fs310/en/ [accessed 2 Mar 2017];
2. World Health Organization. Fact Sheet No. 297. http://www.who.int/mediacentre/factsheets/fs297/en/ [accessed 2 Mar 2017]



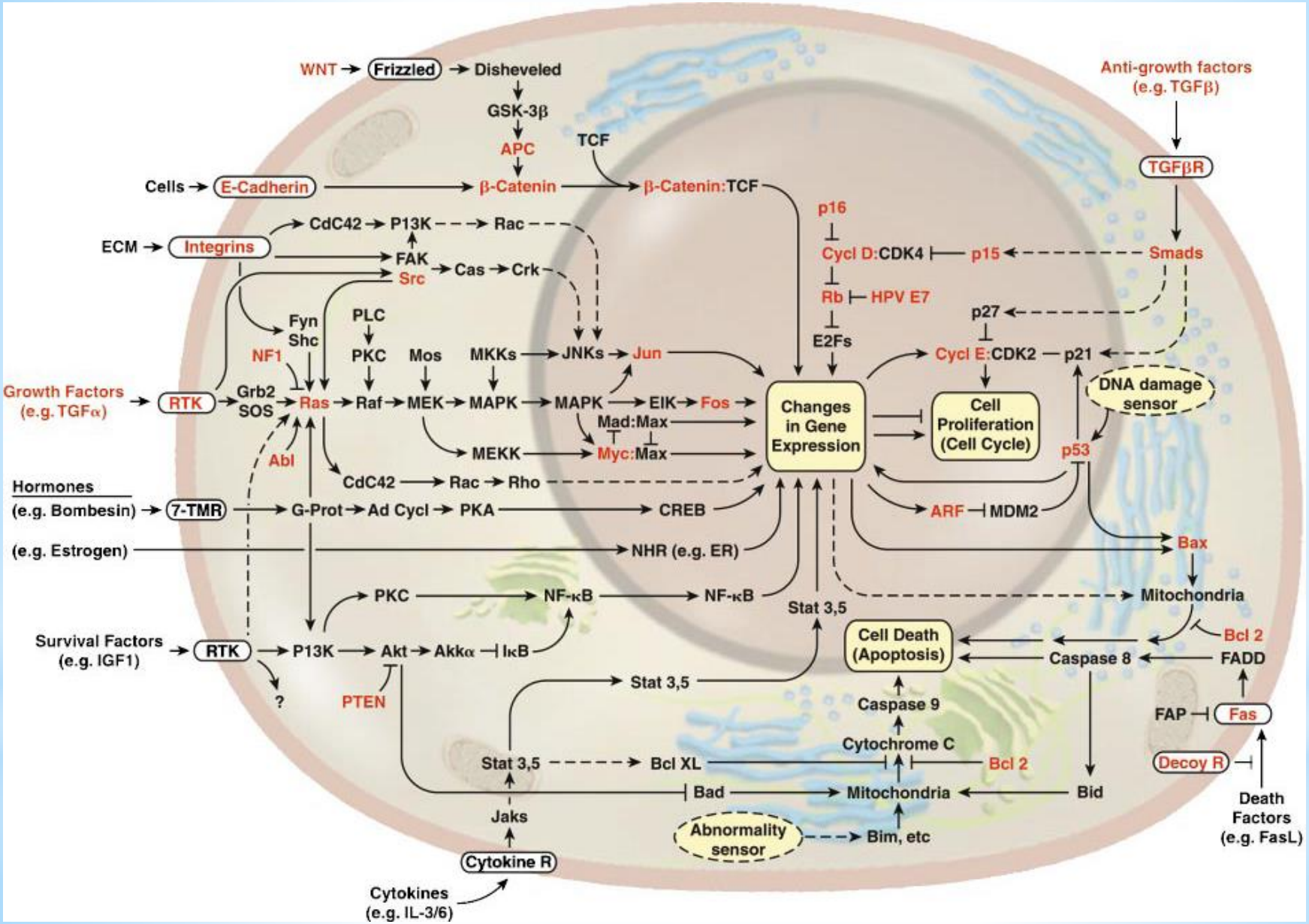
www.thrombosisadviser.com





Cancer

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ã2000 by Cell Press



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ã2000 by Cell Press

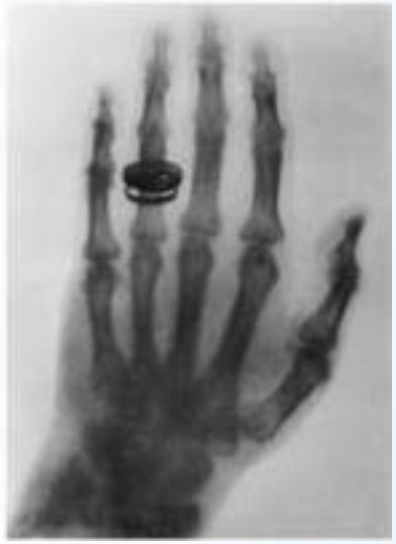
Radiobiology & Radiotherapy

* The study of the interaction of ionizing radiation on living things
  * excitation or ionization

* The medical use of ionizing radiation to treat malignant disease.

* 1895 Roentgen discovery of X-rays
* 1896, 1st medical use reported in Lancet (Dx)
  * X-ray of sailor's backbone to remove piece of a knife

1896, L. Freund treatment of a hairy mole before Vienna Medical Society



1st Therapeutic use

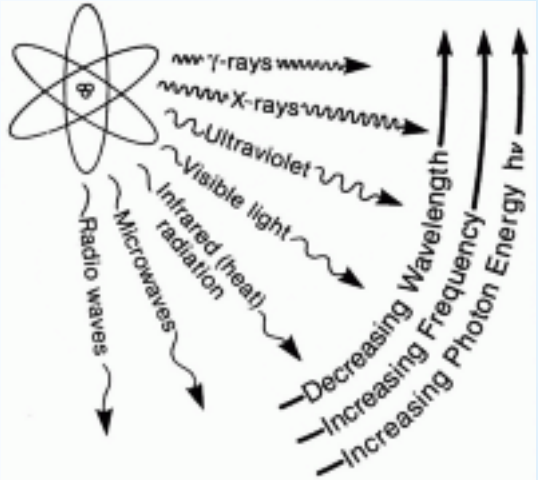
* 1896, , L. Freund treatment of a hairy mole before Vienna Medical Society
* A-H Becquerel discovery of radioactivity emitted by uranium compounds
* Becquerel INADVERTENTLY left radium container in his vest pocket
* 1901, Pierre Curie “radiation burn”

Radiobiology & Radiotherapy

* IR: local release of large amount of energy
* ~ 33eV dissipated / ionizing event, enough to break strong chemical bond
* energy associated C=C bond is 4.9 eV
* Types:
  * Electromagnetic
  * particulate

Electromagnetic Radiations

- X-rays and γ-rays
  - extranuclear and intranuclear production
- X-rays
  - electrical & magnetic energy
    - λν=c
  - Streams of photons/"packets" energy
    - hμ
    - λA=12.4/E(keV)



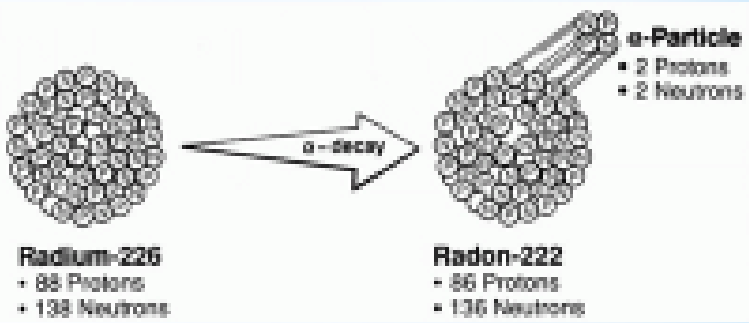
Radiobiology

* Concept of X-rays composed as photons is central in radiobiology
* Energy is deposited in tissues & cells unevenly in discrete packets culminates in biologic change

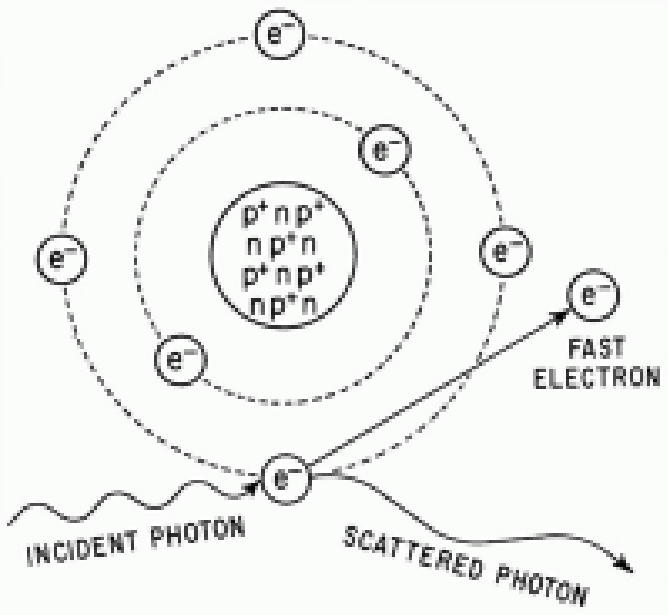
Particulate Radiations

* Electrons, protons, α-particles, neutrons, -π mesons, heavy charged ions
  * small - charged particles accelerated to high energy (betatron or linear accelerator)
  * + charged particles, relatively massive, accelerated to high energy (cyclotron)
  * mass like protons, no electrical charge
  * C, Ne, Fe + charged

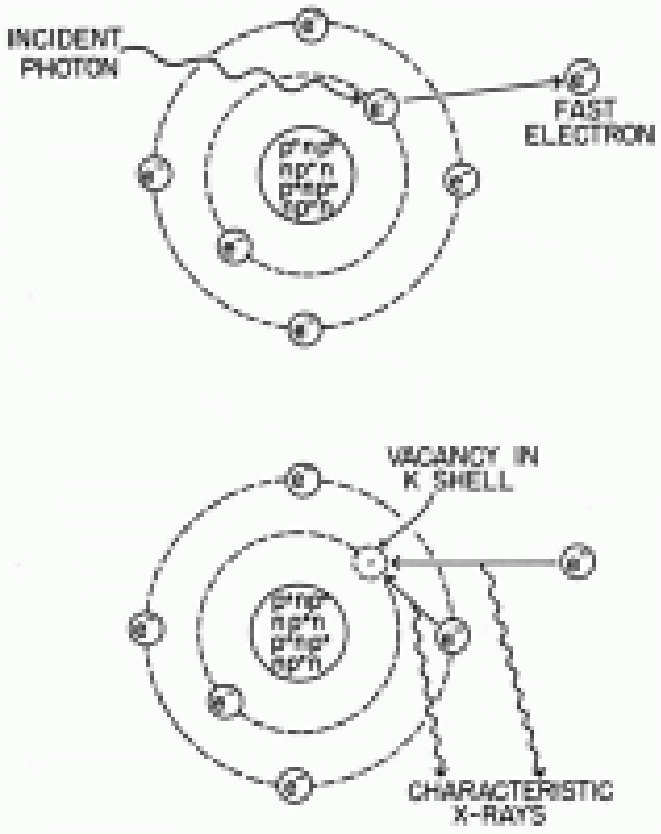
* α-particles (+charged, decay) lung cancer in smokers (10-20,000 cases/year)



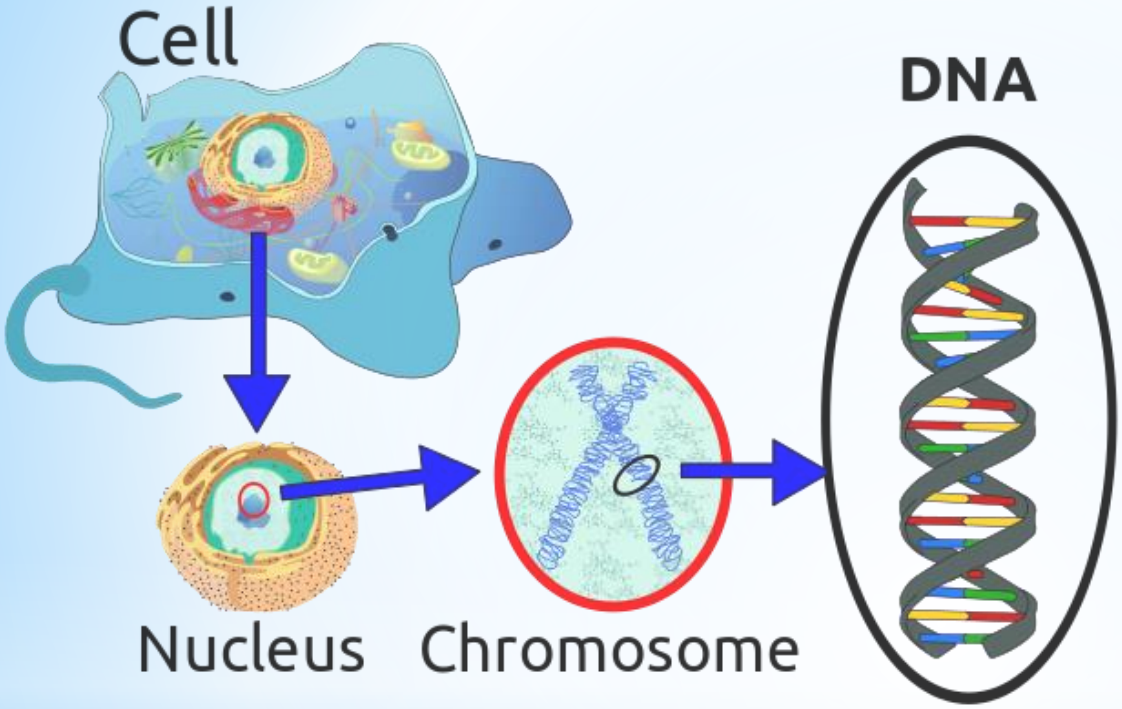
Absorptions of X-rays

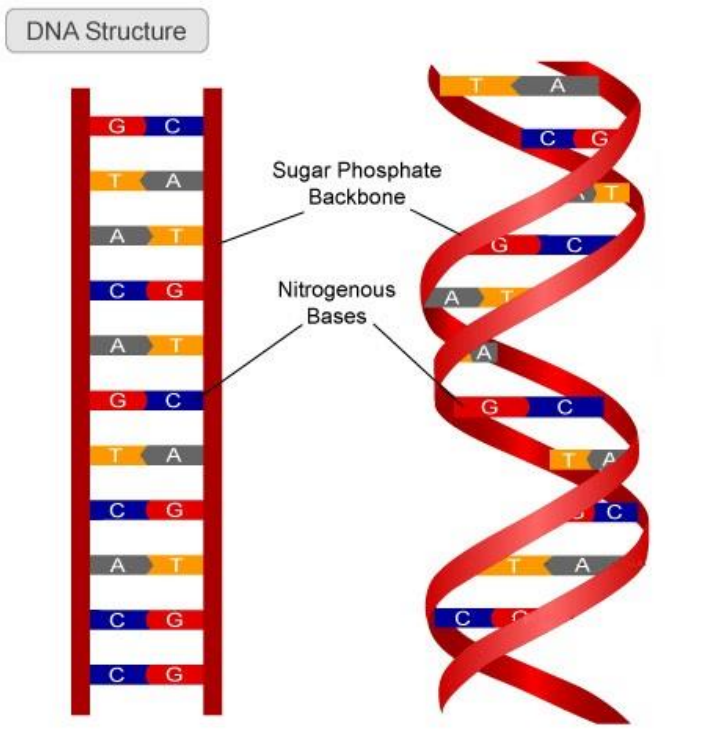


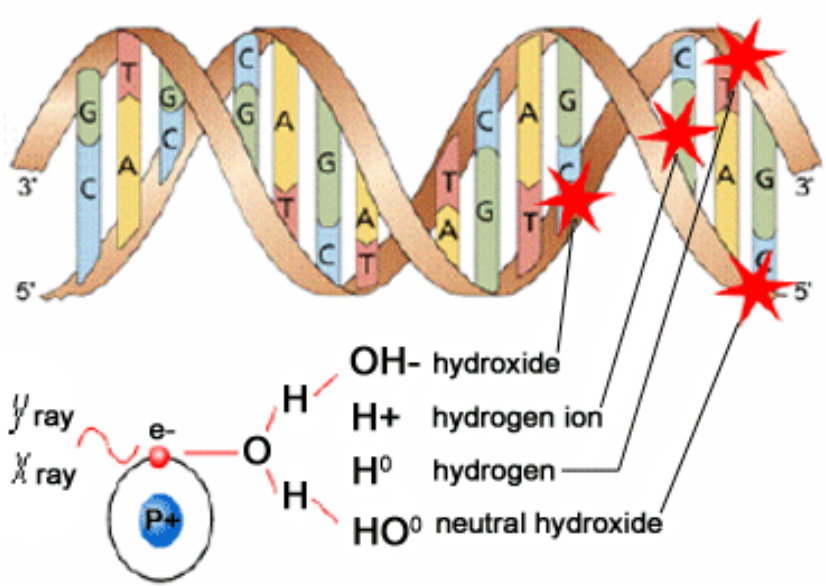
* Absorption of an x-ray photon by the Compton process (Co & linac).
* The photon interacts with a loosely bound planetary electron of an atom of the absorbing
* material. Part of the photon energy is given to the electron as kinetic energy. The photon, deflected from its original direction, proceeds with reduced energy.

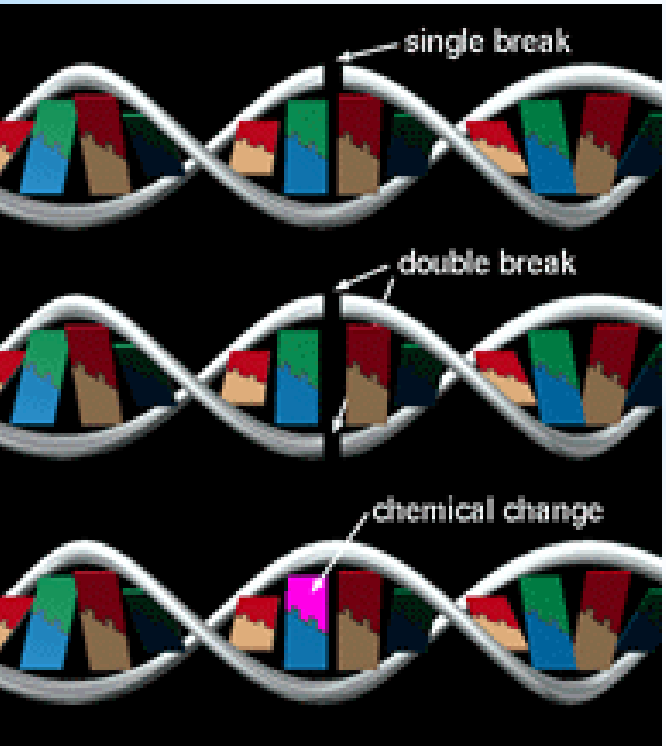


* Absorption of a photon of x- or γ-rays by the Photoelectric process. The interaction involves the photon and a tightly bound orbital electron of an atom of the absorber. The photon gives up its energy entirely; the electron is ejected with a kinetic energy equal to the energy of the incident photon less the binding energy that previously held the electron in orbit **(top). The vacancy is filled either by an electron from an outer**
* orbit or by a free electron from outside the atom **(bottom). If**
* an electron changes energy levels, the difference in energy is
* emitted as a photon of characteristic x-rays. For soft tissue
* these x-rays are of very low energy.


Cell
DNA
Nucleus
Chromosome

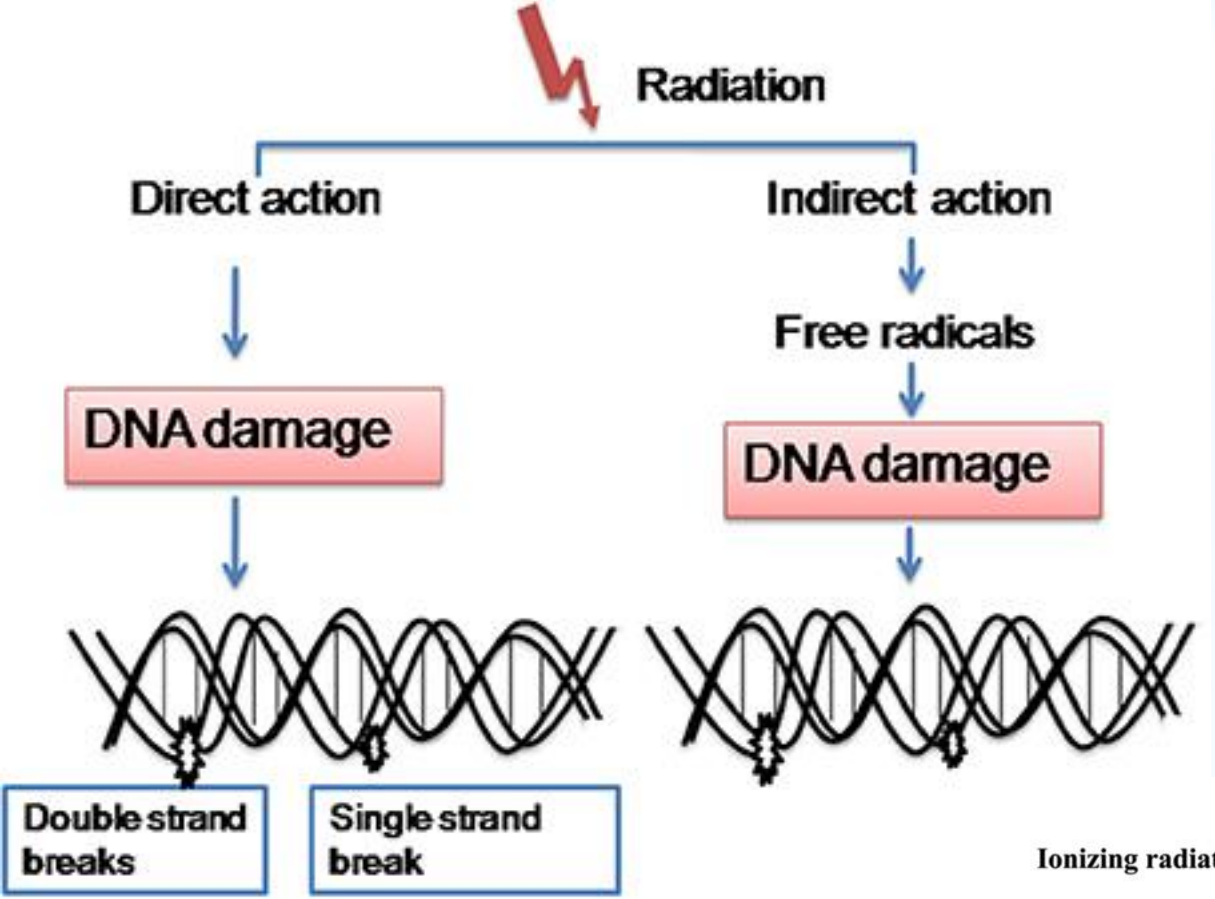

DNA Structure
Sugar Phosphate Backbone
Nitrogenous Bases

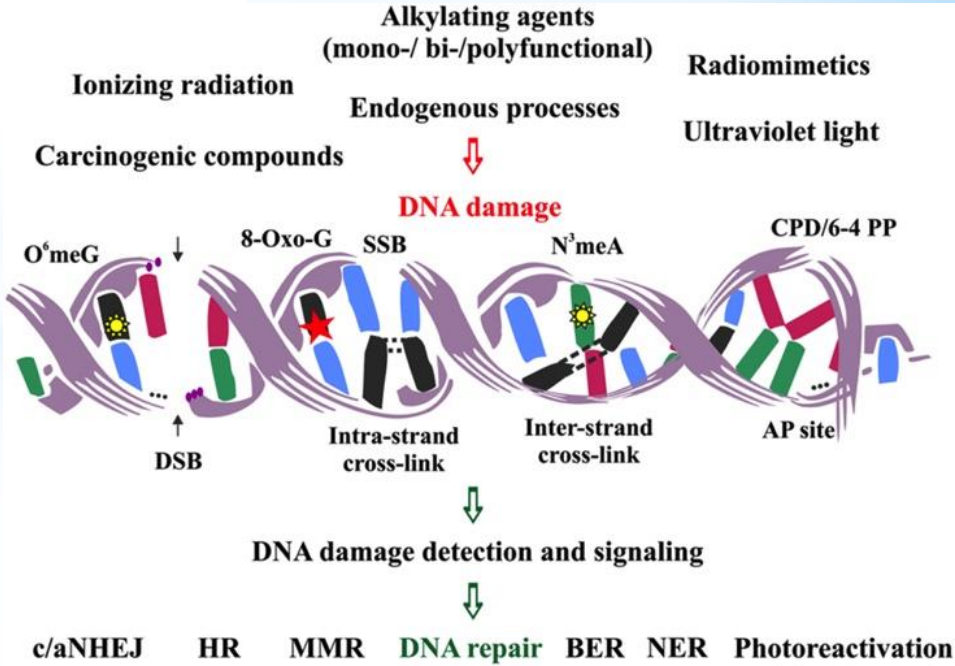


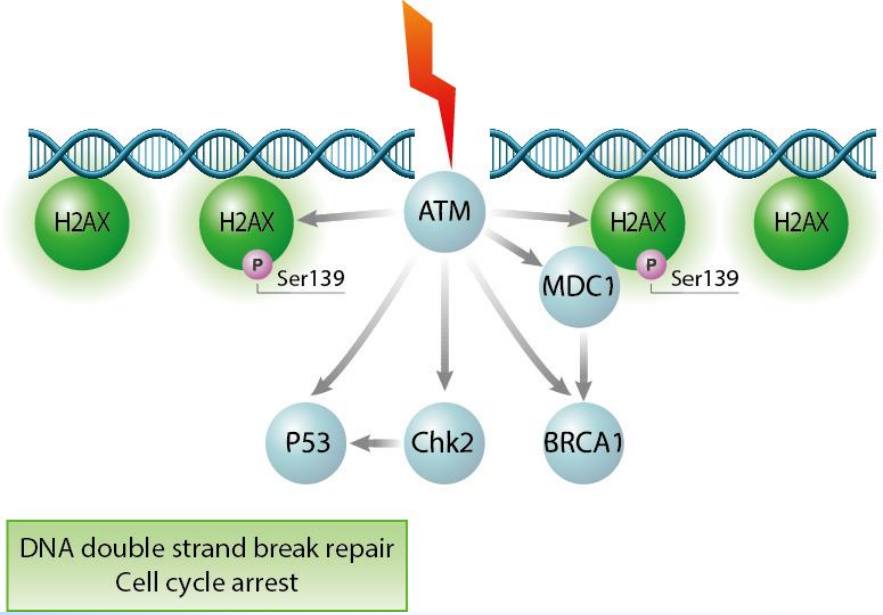


* Action of Radiation

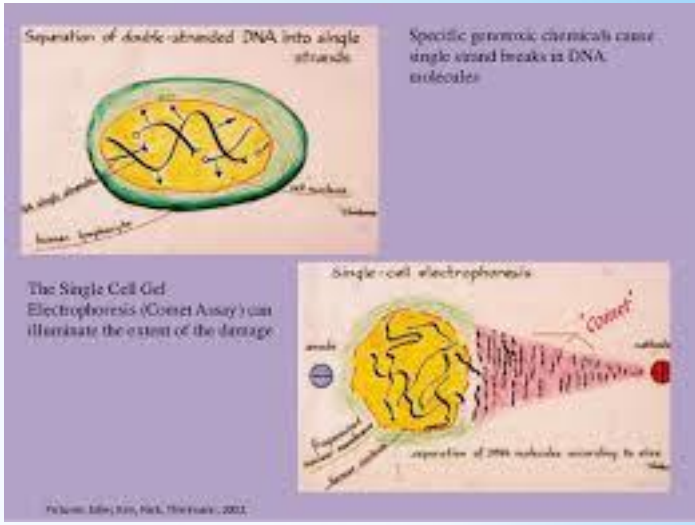
* Direct and indirect actions of radiation. The structure of DNA is shown schematically. In direct action, a secondary electron resulting from absorption of an x-ray photon interacts with the DNA to produce an effect. In indirect action, the secondary electron interacts with, for example, a water molecule to produce a hydroxyl radical (OH·), which in turn produces the damage to the DNA. The DNA helix has a diameter of about 20 Å (2 nm). It is estimated that free radicals produced in a cylinder with a diameter double that of the DNA helix can affect the DNA. Indirect action is dominant for sparsely ionizing radiation, such as x-rays. *S, sugar; P, phosphorus; A, adenine; T, thymine; G, guanine; C, cytosine.*

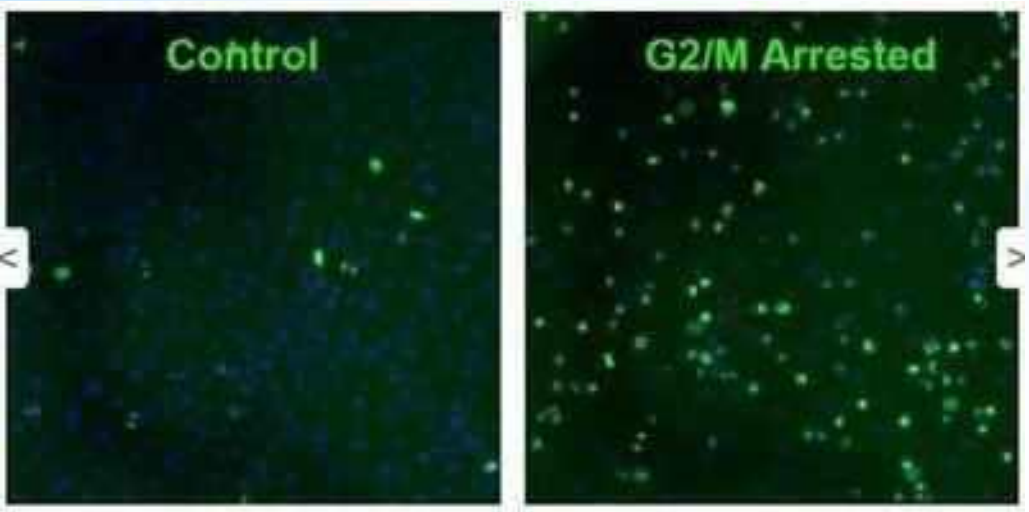

Radiation
Direct action
Indirect action
Free radicals
DNA damage
DNA damage
Double strand breaks
Single strand break

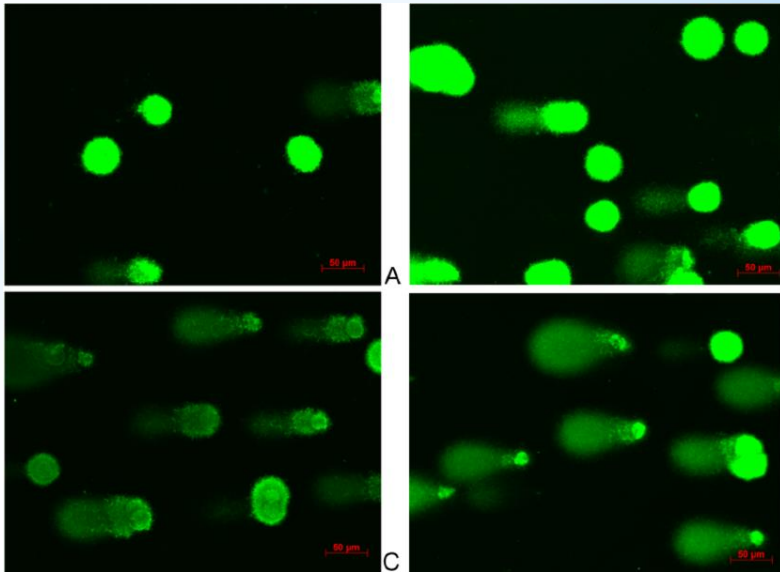

Alkylating agents
(mono-/ bi-/polyfunctional)
Radiomimetics
Ionizing radiation
Endogenous processes
Ultraviolet light
Carcinogenic compounds
DNA damage
O⁶meG
8-Oxo-G
SSB
N³meA
CPD/6-4 PP
DSB
Intra-strand cross-link
Inter-strand cross-link
AP site
DNA damage detection and signaling
c/aNHEJ
HR
MMR
DNA repair
BER
NER
Photoreactivation



DNA double strand break repair
Cell cycle arrest

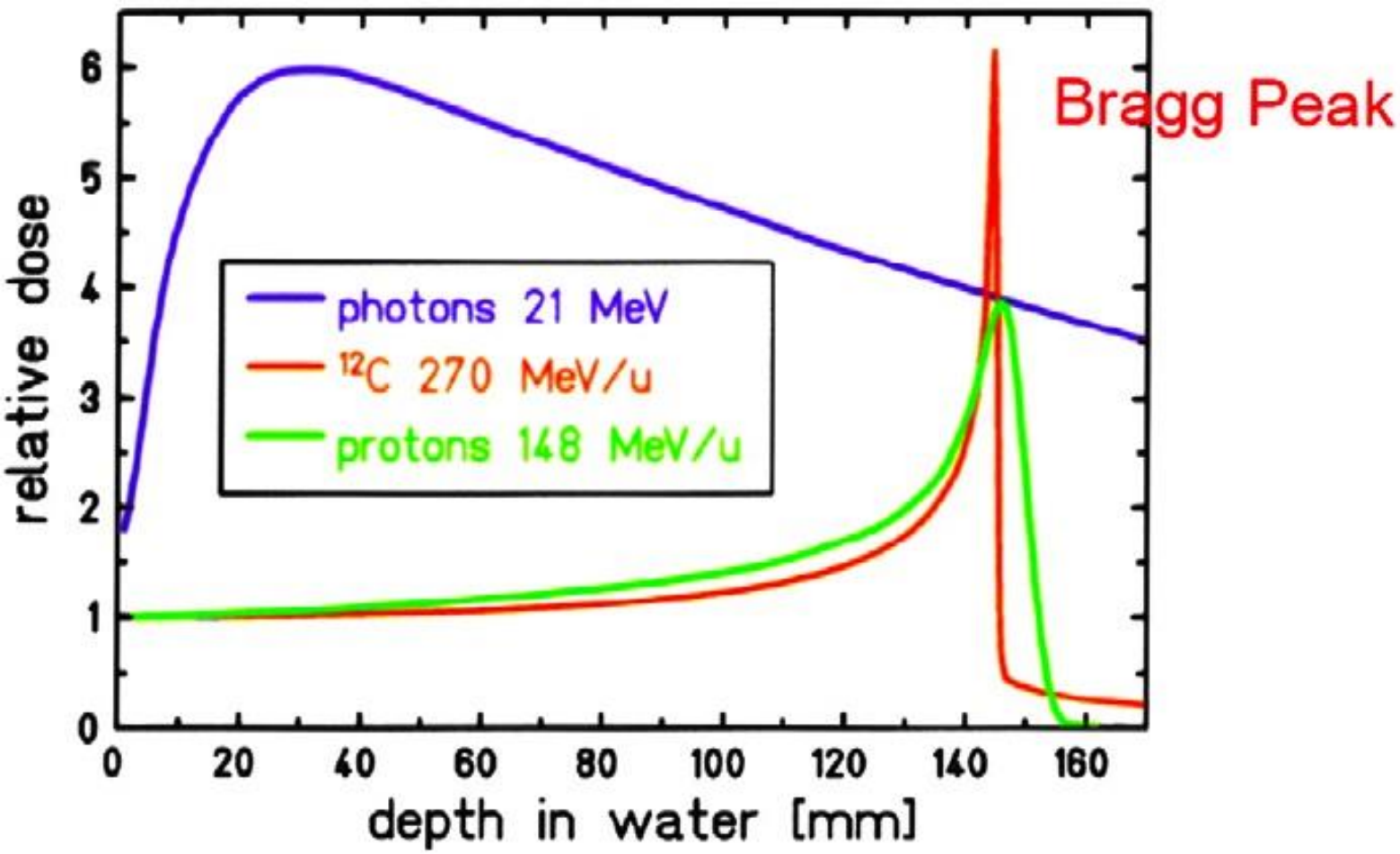






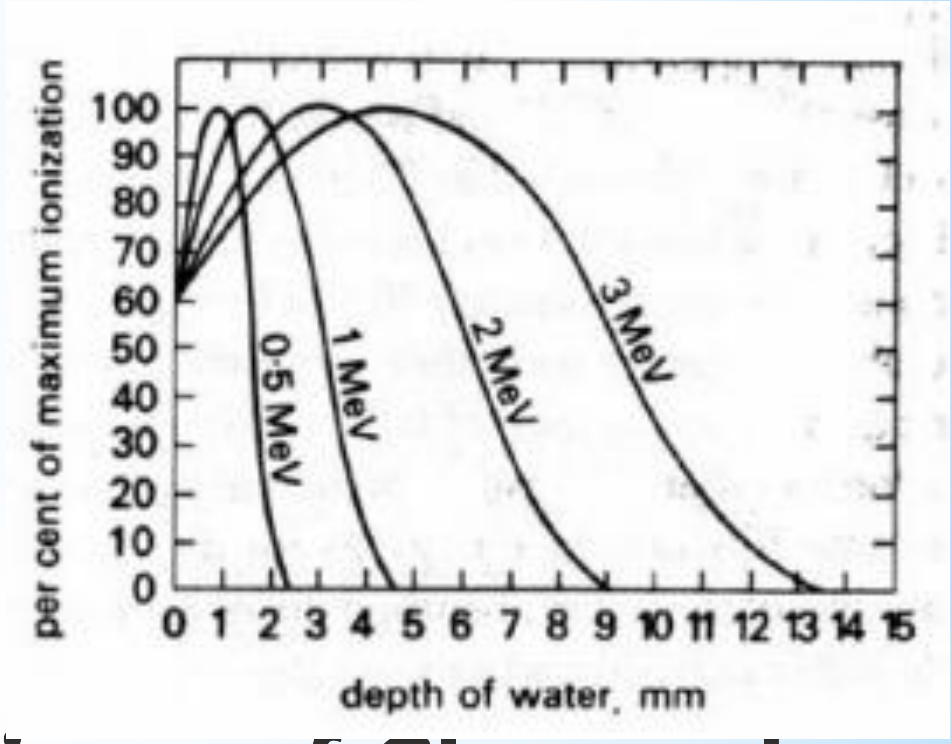
Interactions of Charged Particles

- Ionization and excitation
- Mediated by Coulomb force (electric fields of particle & material)
- Heavy charged particles give rises to nuclear reactions (positrons emitters)
  - Rate of energy loss proportional to square of charged particle and inversely to square of its velocity “Bragg peak”


Bragg Peak
relative dose
depth in water [mm]
photons 21 MeV
12C 270 MeV/u
protons 148 MeV/u
0
1
2
3
4
5
6
0
20
40
60
80
100
120
140
160

Interactions of Charged Particles

* Electrons small masses thus multiple scattering and changes in direction of motion resulting in a “smearing out” of the Bragg peak effect

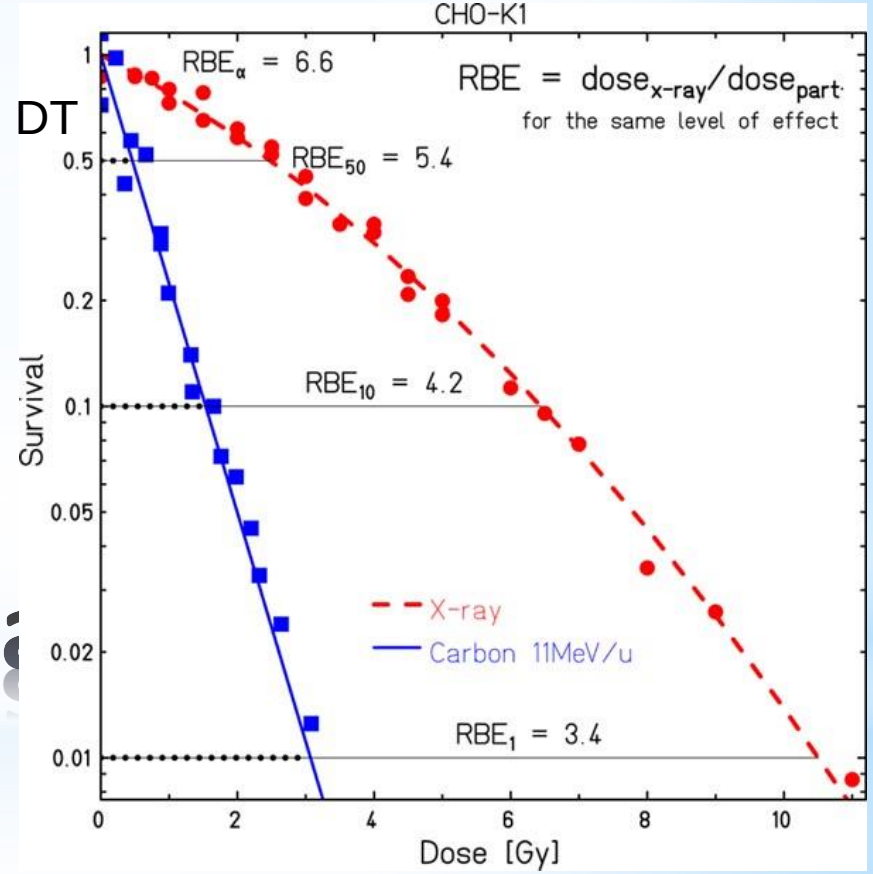


* Neutrons are indirectly ionizing interacting by 2 processes:
  * Recoiling protons: dose deposited in tissue is predominantly from recoil protons, dose absorbed by in fat is 20% > muscle due to differential H content
  * Nuclear disintegrations (charged particles & -rays) give rise to ~ 30% of the tissue dose

* Interactions of Charged Particles

RBE = Dose from reference radiation / Dose from test radiation, DT

Type and Energy Range	Radiation Weighting Factors
X and Gamma rays	1
Electrons	1
Neutrons (energy dependent)	5-20
Protons	5
Alpha Particles	20



*Dose Response Curves

Tumor Radiobiology

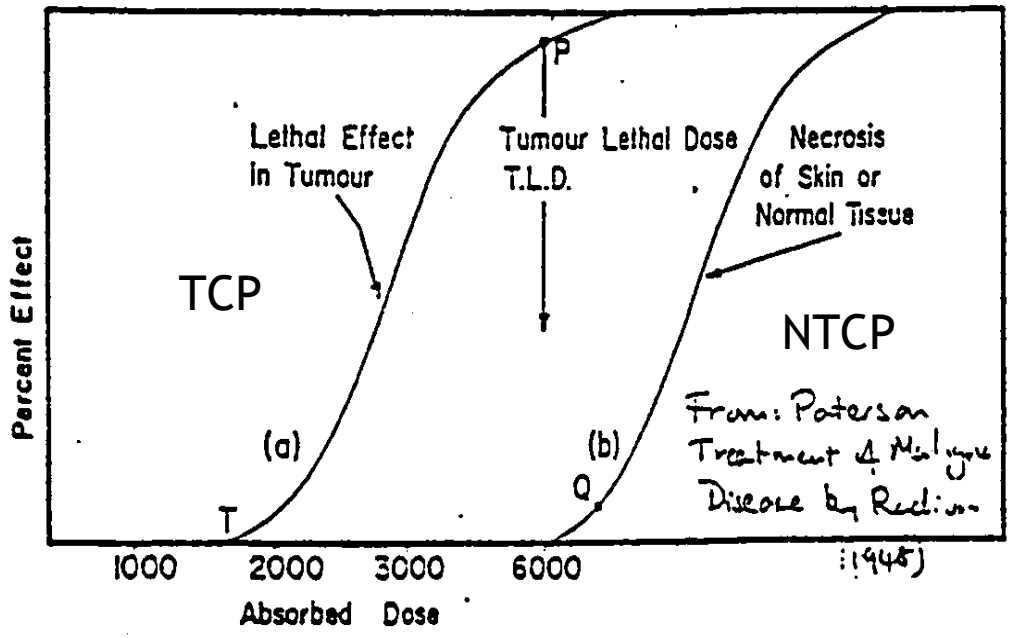
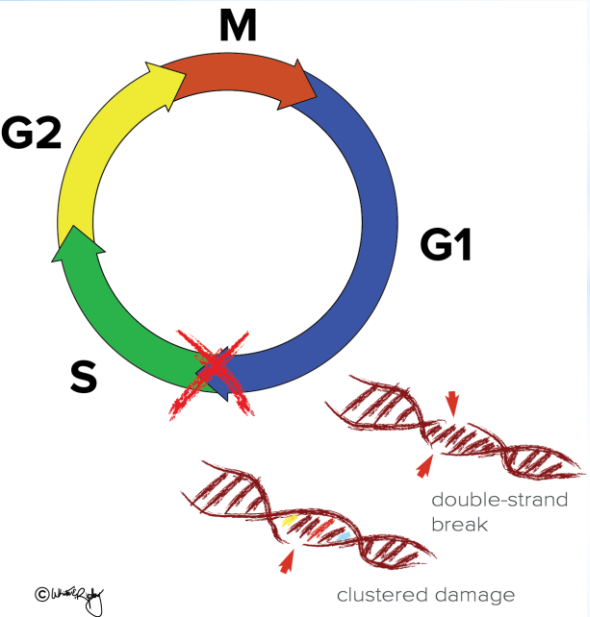


Figure 10.1: Therapeutic ratio.

Why Daily treatments? Four R's of radiotherapy:

* Repair of sub-lethal damage
* Re-oxygenation
* Repopulation
* Redistribution

* **Repair** of DNA damage: of “sublethal” damage human tumors/normal tissues difference in radiosensitivity and radiocurability is based on differences in capacity to repair of sublethal damage.
* **Redistribution** in the cell cycle.
  * G1 (gap, inactivity, before S), S (DNA synthesis) , G2 (2nd gap between S and M) and M (mitosis).
  * Radiosensitivity varies along the cell cycle, S being the most resistant phase, and G2 and M the most sensitive.
  * Cells surviving an exposure are synchronised in a resistant cell cycle phase low sensitivity (G1). Followed by together into S and then to the more sensitive G2 and M phases.
* Repopulation.
  * Surviving cells keep proliferating, increasing the number of clones, i.e. the number that must eventually be sterilised to eradicate cancer.
  * Detrimental in tumor: “resistance”
  * Normal tissues stem cells also proliferate, repairing sublethal damage
* Reoxygenation
  * Of hypoxic core, “onion peel effect” of fractionated RT



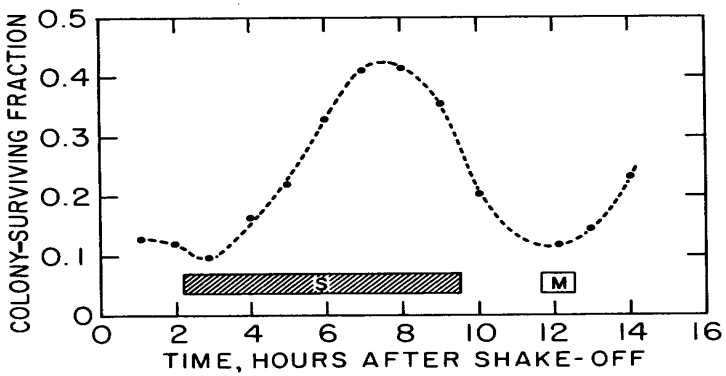
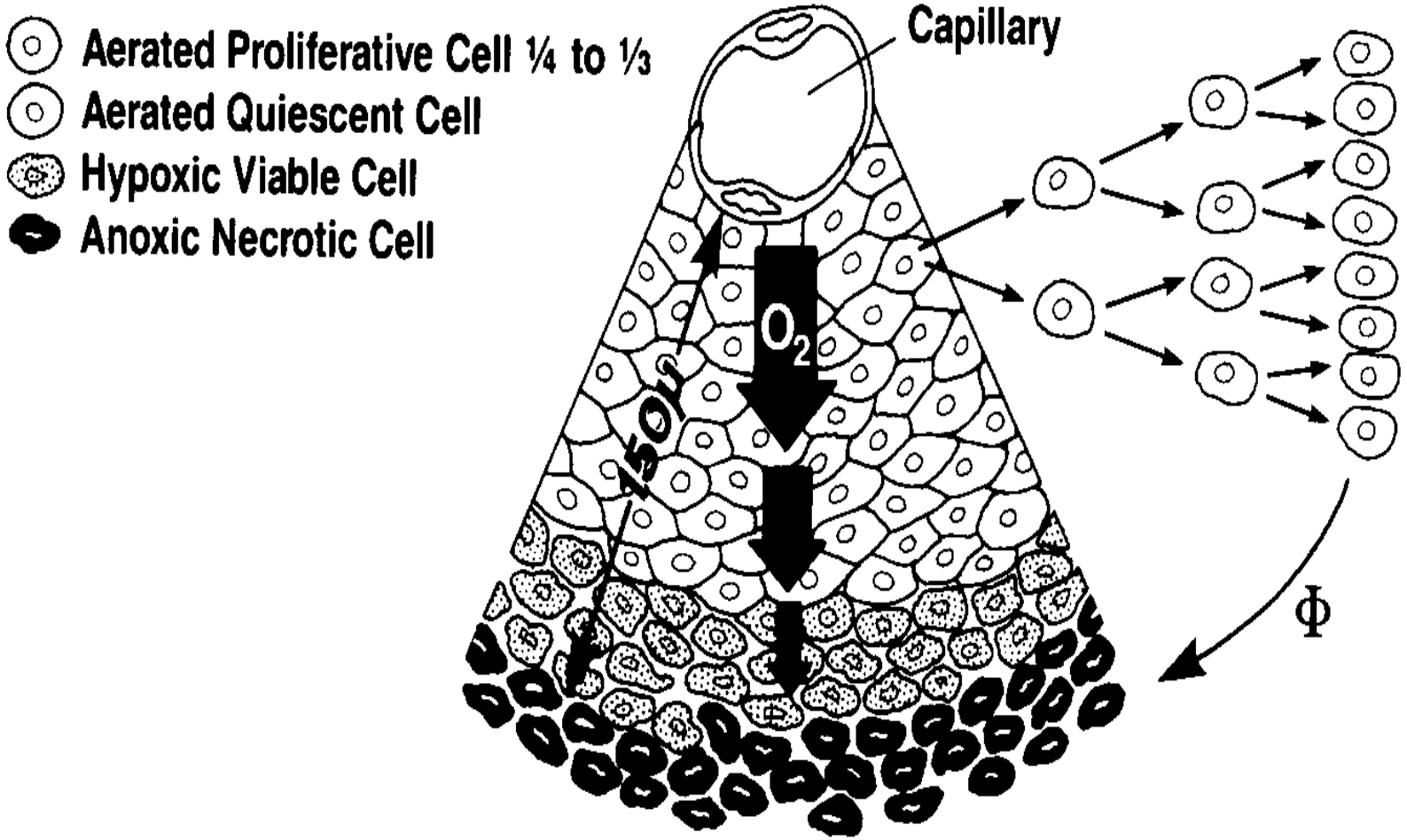


Figure 5–6. Fraction of Chinese hamster cells surviving a dose of 660 rads (6.6 Gy) of x-rays as a function of time. Time zero corresponds to the harvesting of mitotic cells. The cell-surviving fraction increases to a maximum late in *S*. (Redrawn from Sinclair WK, Morton RA: Radiat Res 29:450–474, 1966)

*Tumor Oxygenation



Effect of Oxygen

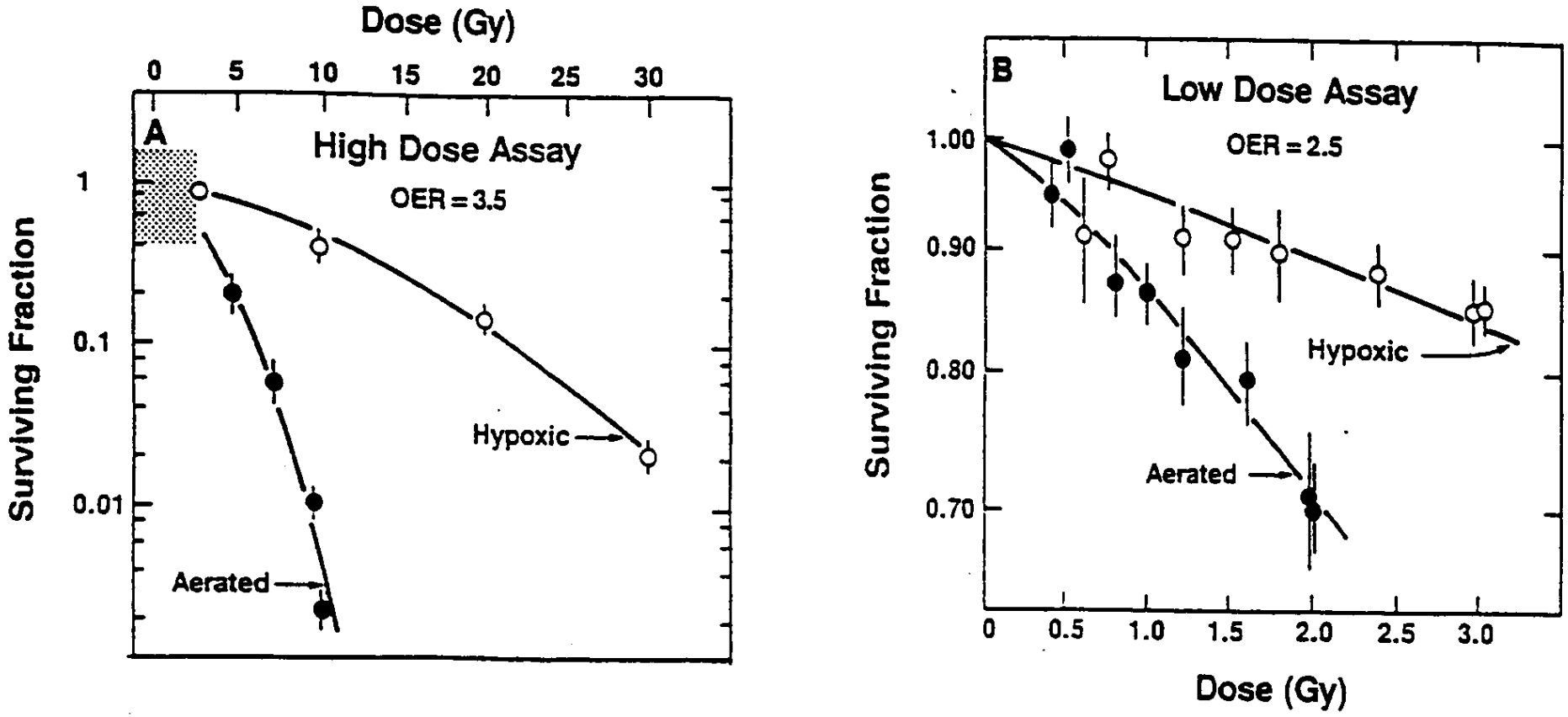
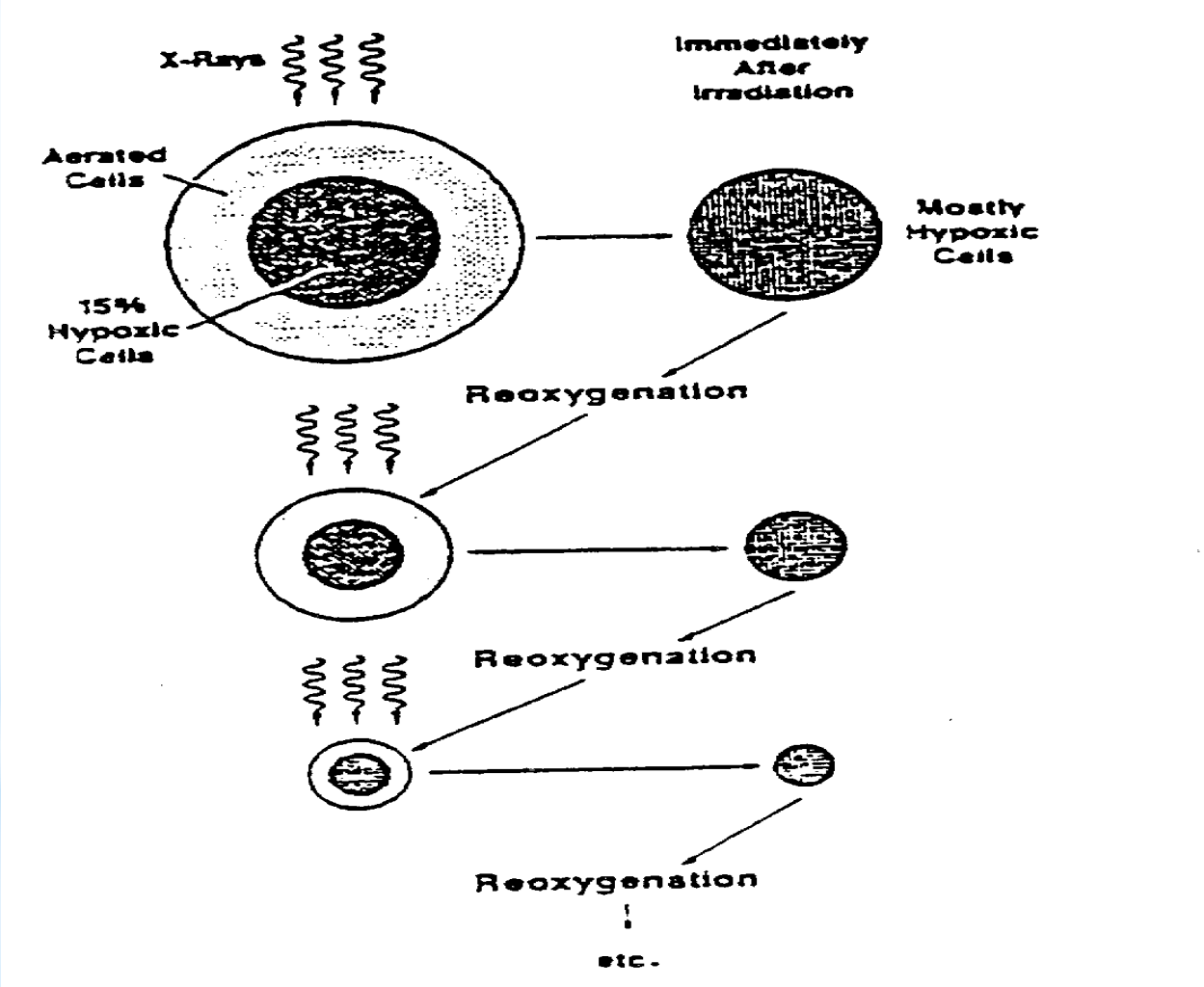
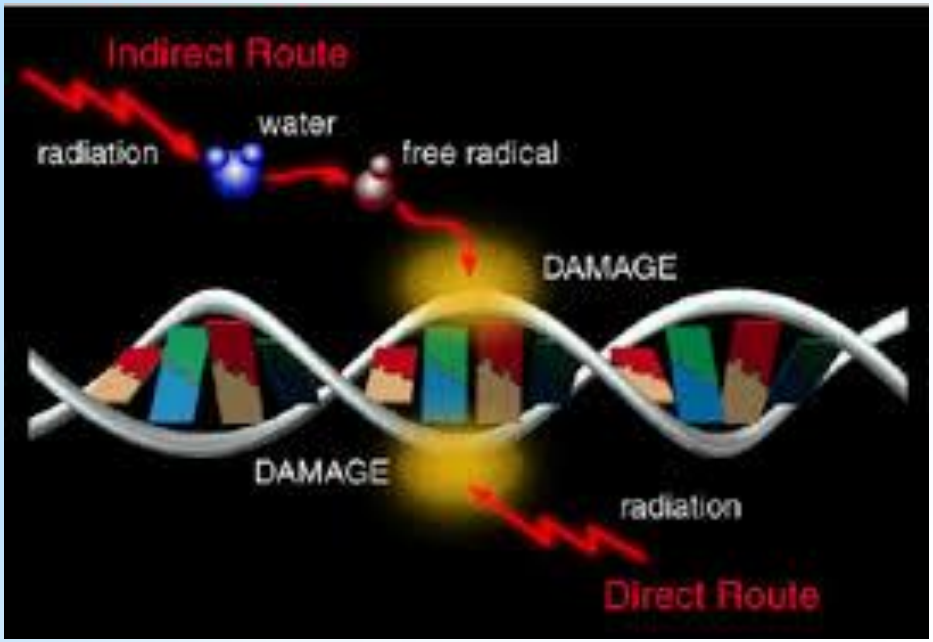


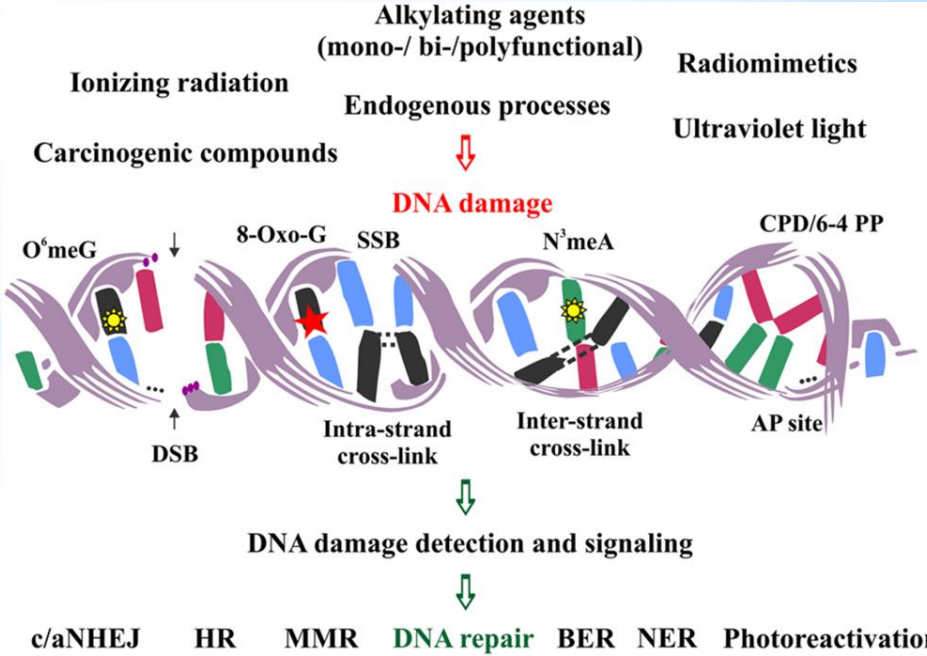
Figure 5.25: For sparsely ionizing radiation (x- and γ- rays) the OER is 2.5-3.0 at higher doses at which oxygen is dose modifying. At lower doses < 2.0 Gy, it may have a value of about 2.0.

* Re-oxygenation

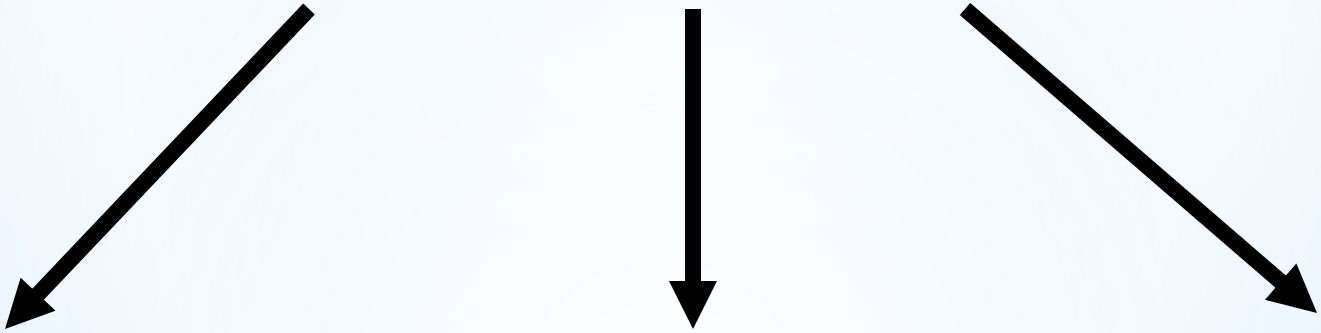


*Mechanism of cytotoxicity





Chromosomal Damage



Apoptosis

Reproductive death

Necrosis

Cell survival curves

Cell Radiation Biology

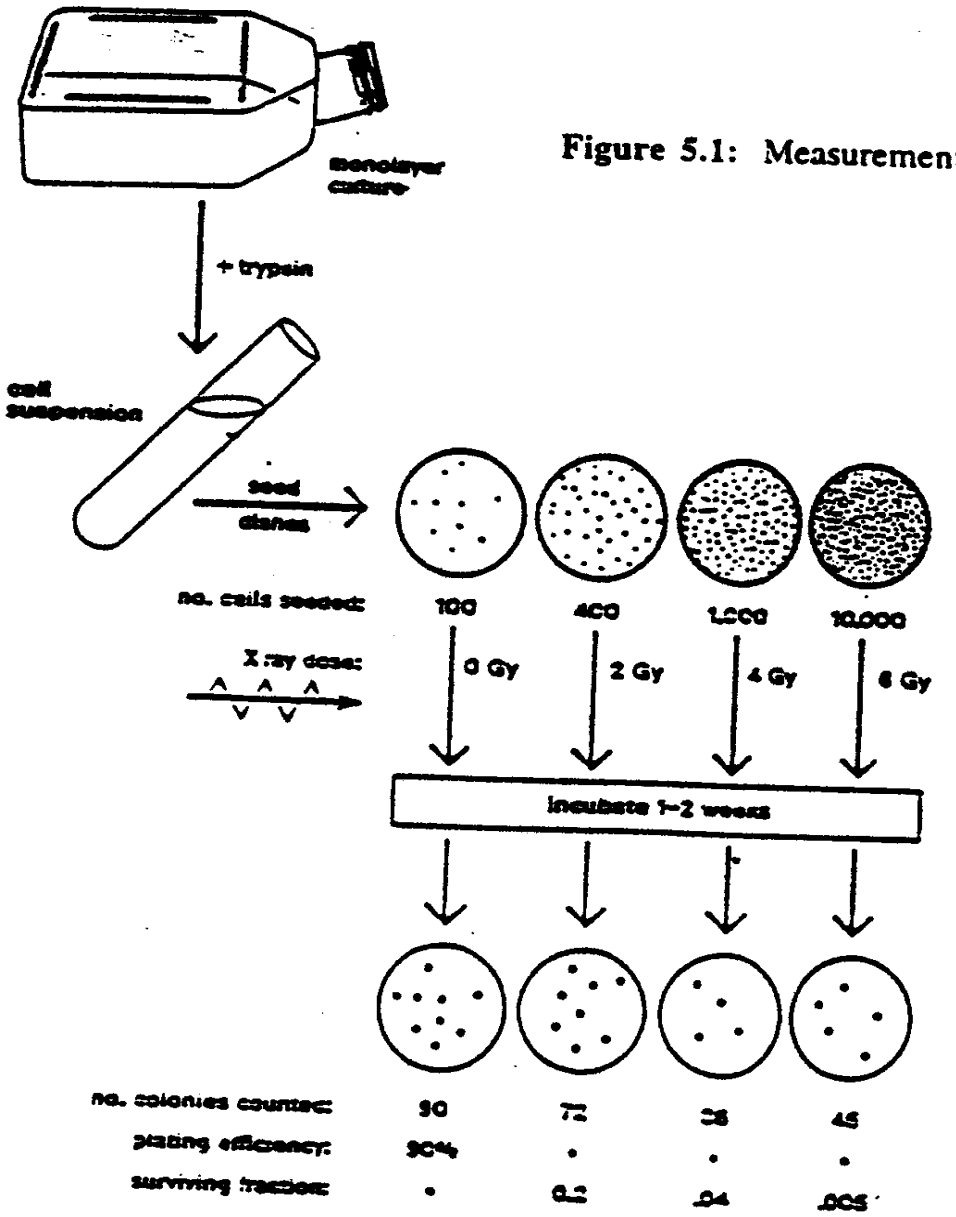
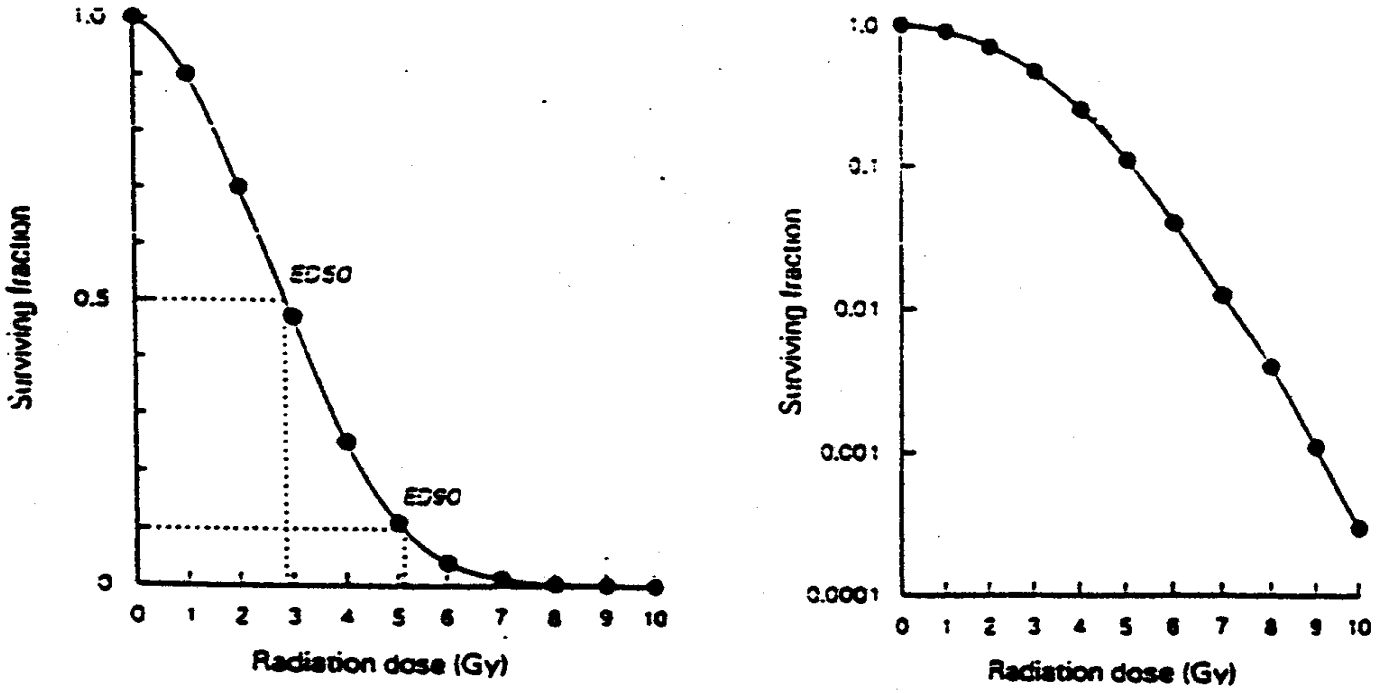


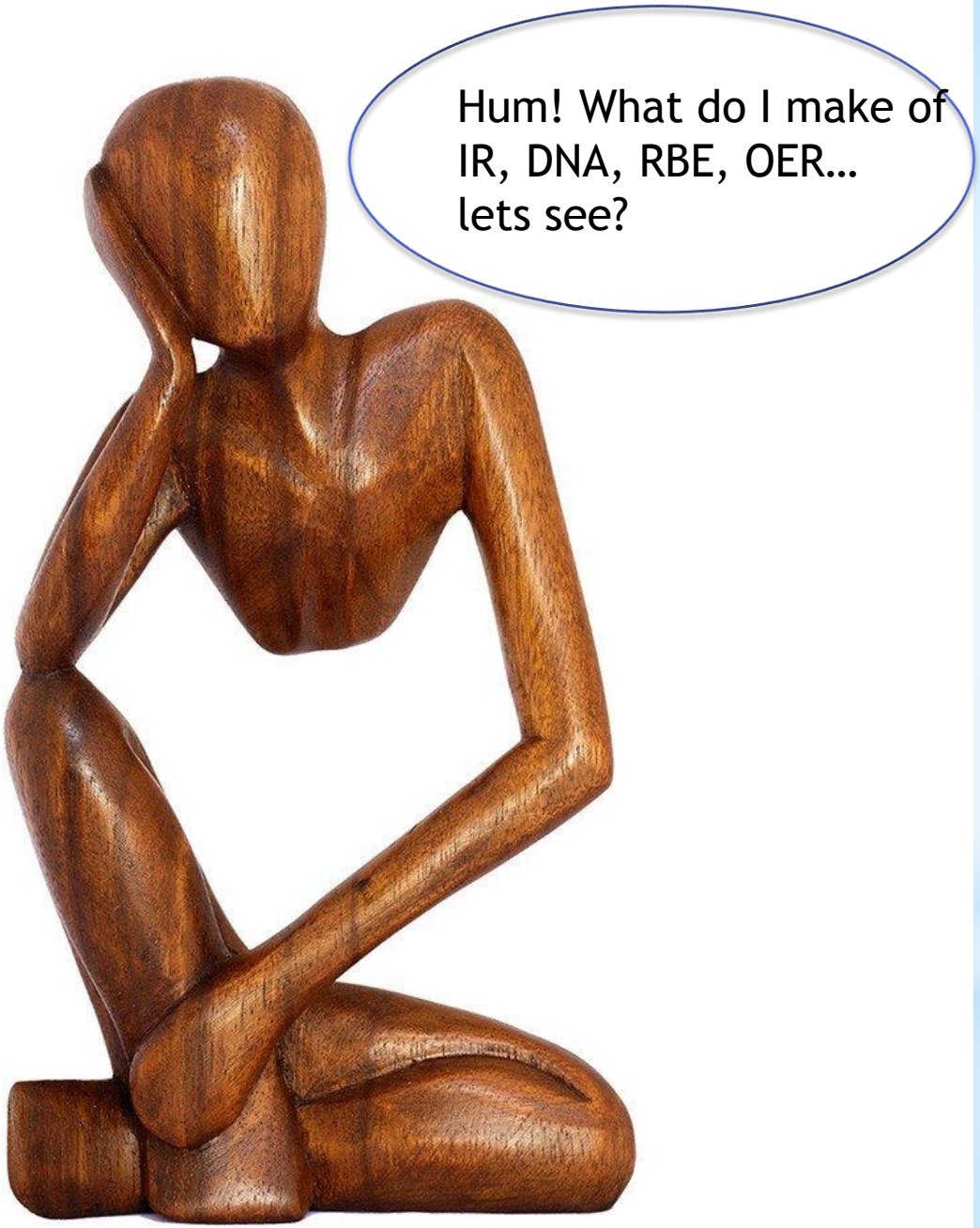
Figure 5.1: Measurement of cell survival.



(a): linear scale

(b): same data on a logarithmic scale

Figure 5.2: Typical cell survival curve for mammalian cells irradiated in tissue culture.


Hum! What do I make of IR, DNA, RBE, OER… lets see?

International Journal of
Radiation Oncology
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Biology Contribution

ZRBA1, a Mixed EGFR/DNA Targeting Molecule, Potentiates Radiation Response Through Delayed DNA Damage Repair Process in a Triple Negative Breast Cancer Model

Mitra Heravi, PhD,[*,†,‡] Slawomir Kumala, PhD,[†,‡] Zakaria Rachid, PhD,[§] Bertrand J. Jean-Claude, PhD,[§] Danuta Radzioch, PhD,[*] and Thierry M. Muanza, MSc, MD[†,‡]

*Departments of *Human Genetics and [†]Radiation Oncology, McGill University; [‡]Segal Cancer Center, Jewish General Hospital; and [§]Cancer Drug Research Laboratory, McGill University Health Center, Montreal, Canada*

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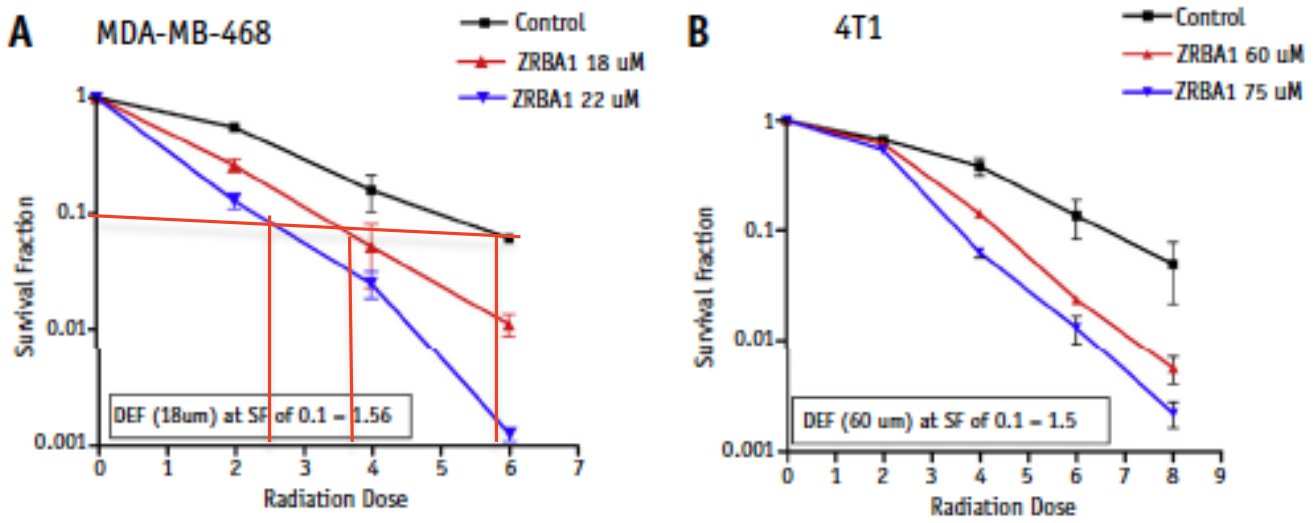

Fig. 1. Analysis of response of (a) MDA-MB-468 cells and (b) 4T1 cells to the combination of ZRBA1 and radiation using clonogenic assays. Before irradiation, cells were exposed for 2 hours to 18 μM ZRBA1, and colony-forming efficiency was determined as described in Methods and Materials. Data represent means and standard deviation from 3 independent experiments. DEF = dose enhancement factor.

(DEF), which is the ratio of the radiation doses at survival fraction of 0.1 of non–drug-treated cells to drug treated cells (Supplementary Methods, available online at

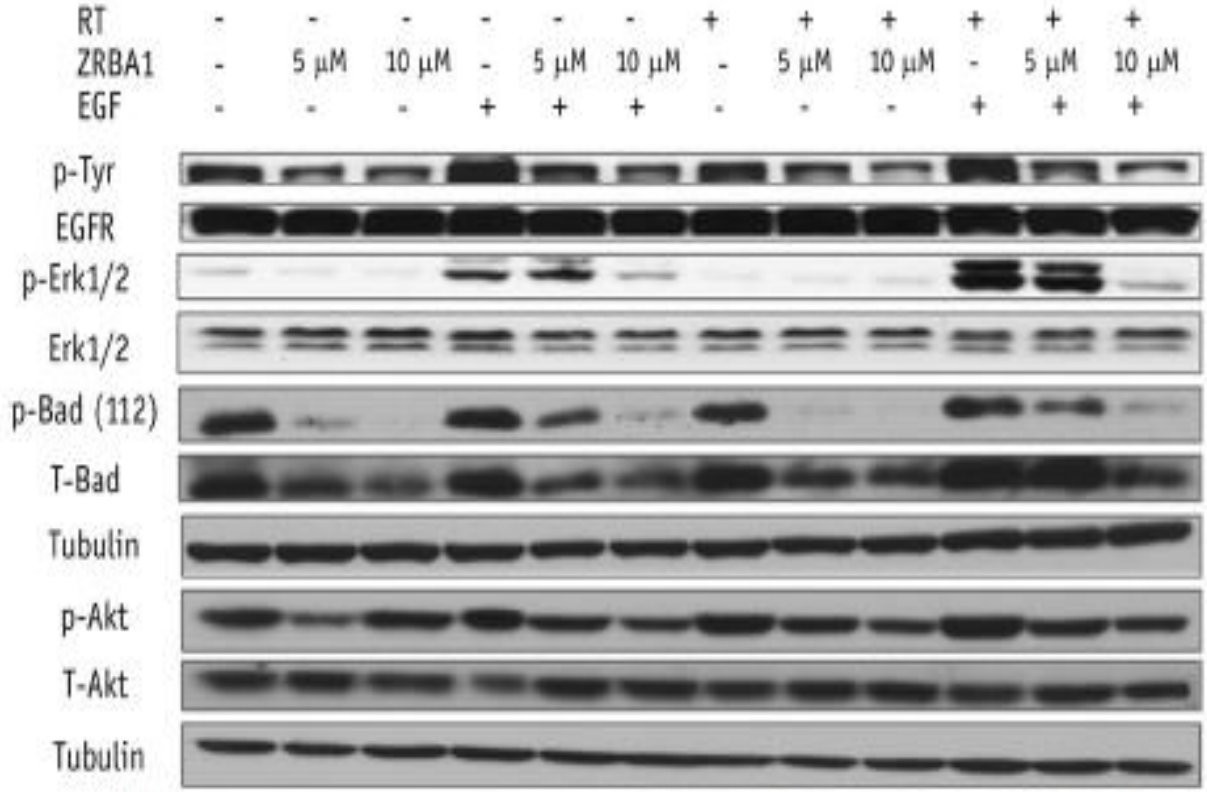

Fig. 2. ZRBA1 inhibits EGFR phosphorylation and downstream MAPK pathway signaling. MDA-MB-468 cells were serum starved for 18 hours and treated with ZRBA1, radiation (RT), or both, or stimulated with epidermal growth factor (EGF) as indicated. Cell lysates were prepared within 1 hour and analyzed by Western blot.

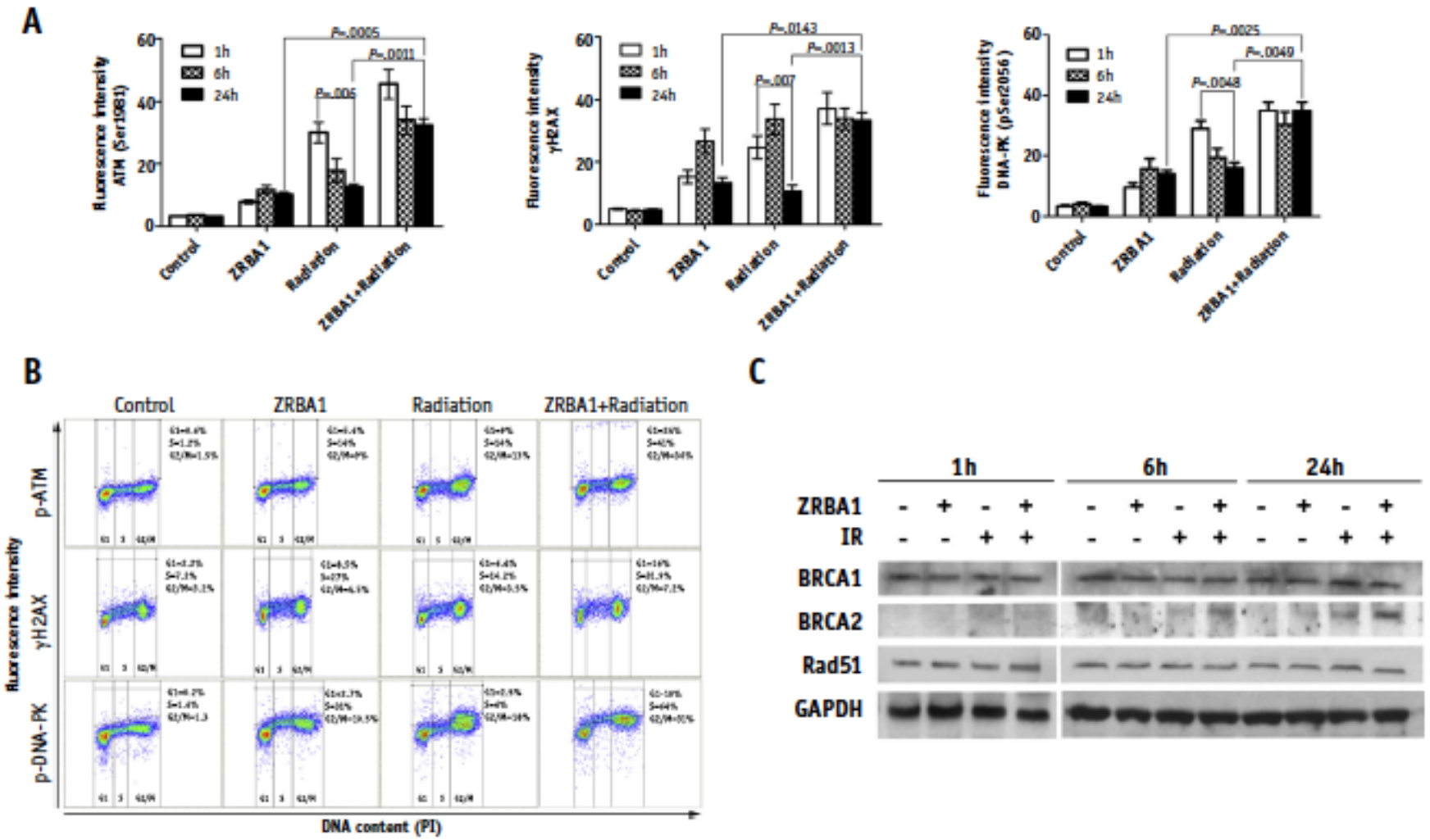

Fig. 4. DNA double-strand breaks repair analysis. (a) Flow cytometric analysis of level of phosphorylated ATM (Ser1981), H2AX (Ser193), and DNA-PKcs (ser2056) in MDA-MB-468 cells. Fluorescence intensity indicates the relative amount of phosphorylation of proteins 1 hour and 24 hours after treatment. (b) Distribution of ATM (Ser1981), H2AX (Ser193), and DNA-PKcs (ser2056) throughout the cell cycle 24 hours after treatment. (C) Analysis of the same cells by Western blot to determine levels of BRCA1, BRCA2, and Rad51 proteins.

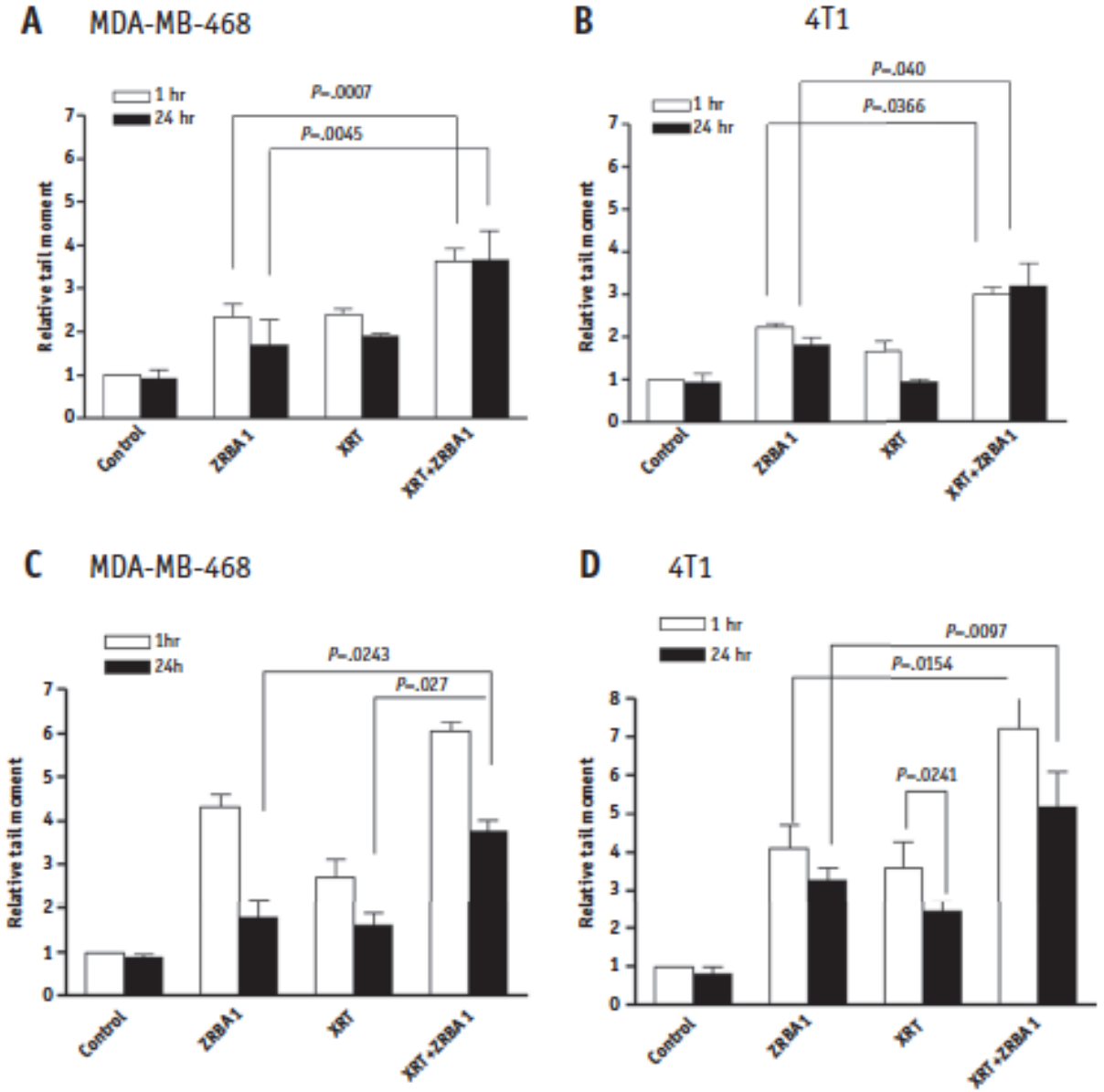

Fig. 3. Analysis of DNA damage induced by ZRBA1, radiation (XRT), or both. Cells were treated and analyzed by microelectrophoresis as described in Methods and Materials. Double strand breaks induction or repair determined by neutral comet assays in MDA-MB-468 (a) and 4T1 (b) cells. (C, D) Detection of single strand breaks and alkali labile sites determined by alkaline comet assays in MDA-MB-468 (c) and 4T1 (d) cells. Data are means and standard deviations of 3 independent experiments.

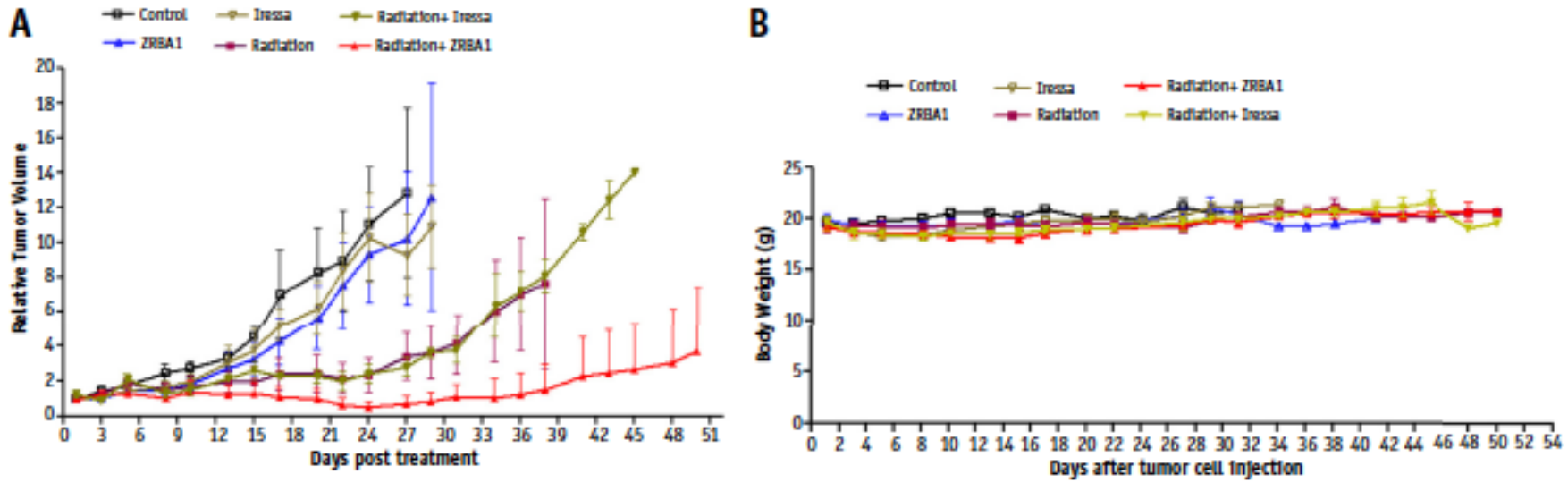

Fig. 5. (a) Tumor growth delay assay. ZRBA1 started to be given to the animals 3 days before radiation, on the same days of irradiation, and continued for 1 day after irradiation. Radiation was delivered in 3 fractions of 5 Gy. Each experimental group contained 5 mice. Tumor volume was calculated by $(L \times W^2)/2$ and normalized by dividing the tumor volume of each animal in treatment groups by the mean tumor volume of the same group. (b) Variations of body weight of mice treated with ZRBA1 or Iressa and radiation alone and the combined treatments. Error bars = standard equivalent of the mean.

Table 1 Tumor growth delay of each treatment group

Treatment group	Days after treatment
Control	11.5
Iressa	13
ZRBA1	14
Radiation	26
Radiation + Iressa	27.5
Radiation + ZRBA1	47

Mice that received the combined treatments had a growth delay almost 2 times and 3 times more than the irradiated-only and ZRBA1-only treated groups, respectively (47 vs 26 days and 14 days).

Radiotherapy delivery :

- External beam radiotherapy:
  - Photons:
    - X-rays: Linear accelerators.
    - γ-rays: Cobalt machines.
  - Particles:
    - Electrons.
    - Neutrons.
    - Protons.
- Brachytherapy:
  - Interstitial.
  - Intracavitary.
  - Intraluminal.

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REVIEW

Back to the future: the history and development of the clinical linear accelerator

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Abstract

The linear accelerator (linac) is the accepted workhorse in radiotherapy in 2006. The first medical linac treated its first patient, in London, in 1953, so the use of these machines in clinical practice has been almost co-existent with the lifetime of *Physics in Medicine and Biology*. This review is a personal selection of things the authors feel are interesting in the history, particularly the early history, and development of clinical linacs. A brief look into the future is also given. One significant theme throughout is the continuity of ideas, building on previous experience. We hope the review might re-connect younger radiotherapy physicists in particular with some of the history and emphasize the continual need, in any human activity, to remain aware of the past, in order to make best use of past experience when taking decisions in the present.

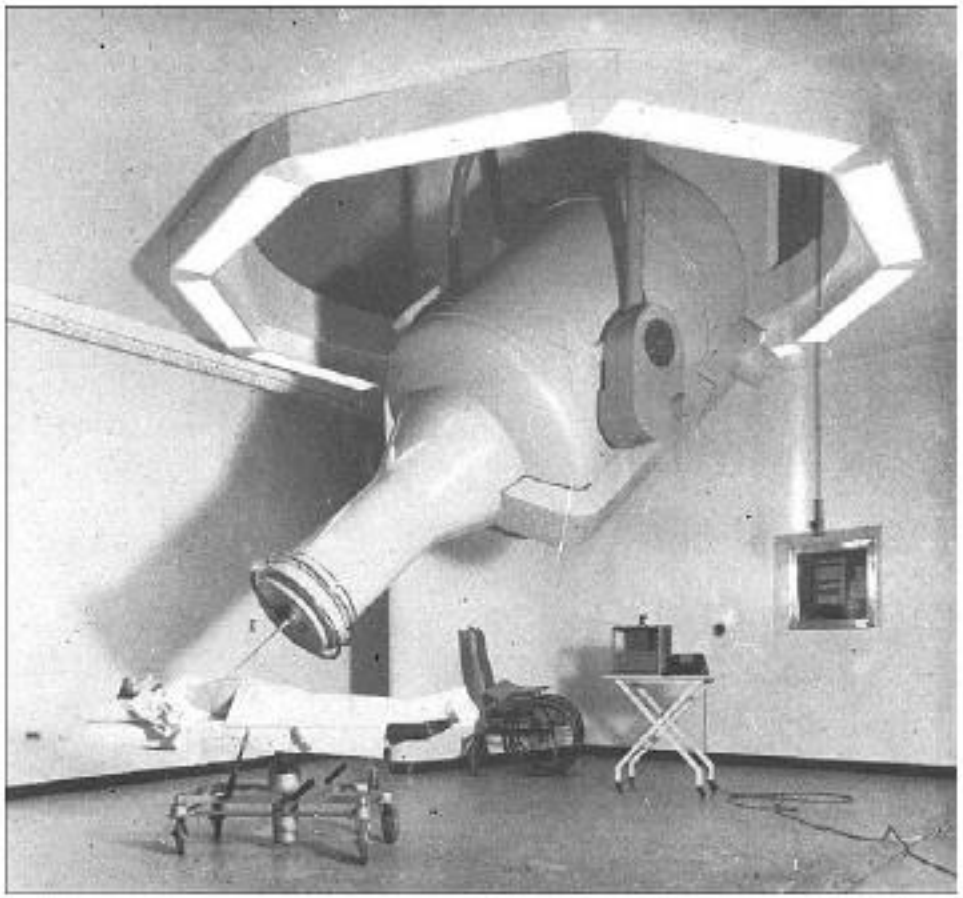


Figure 2. A 4 MeV resonant transformer unit.

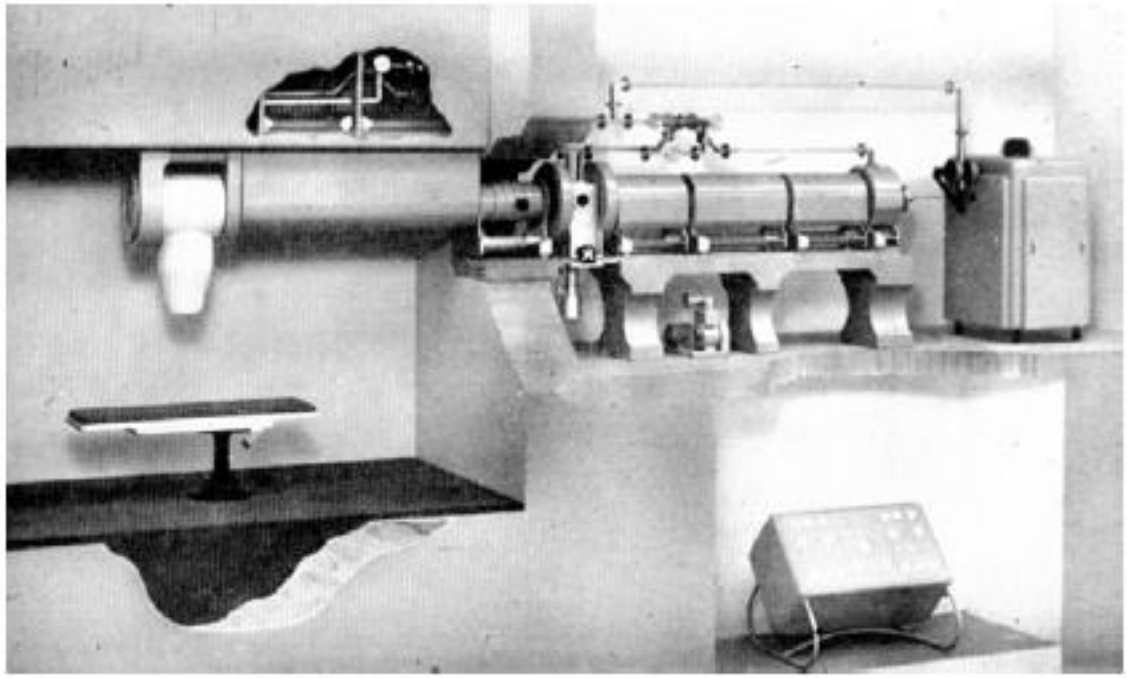
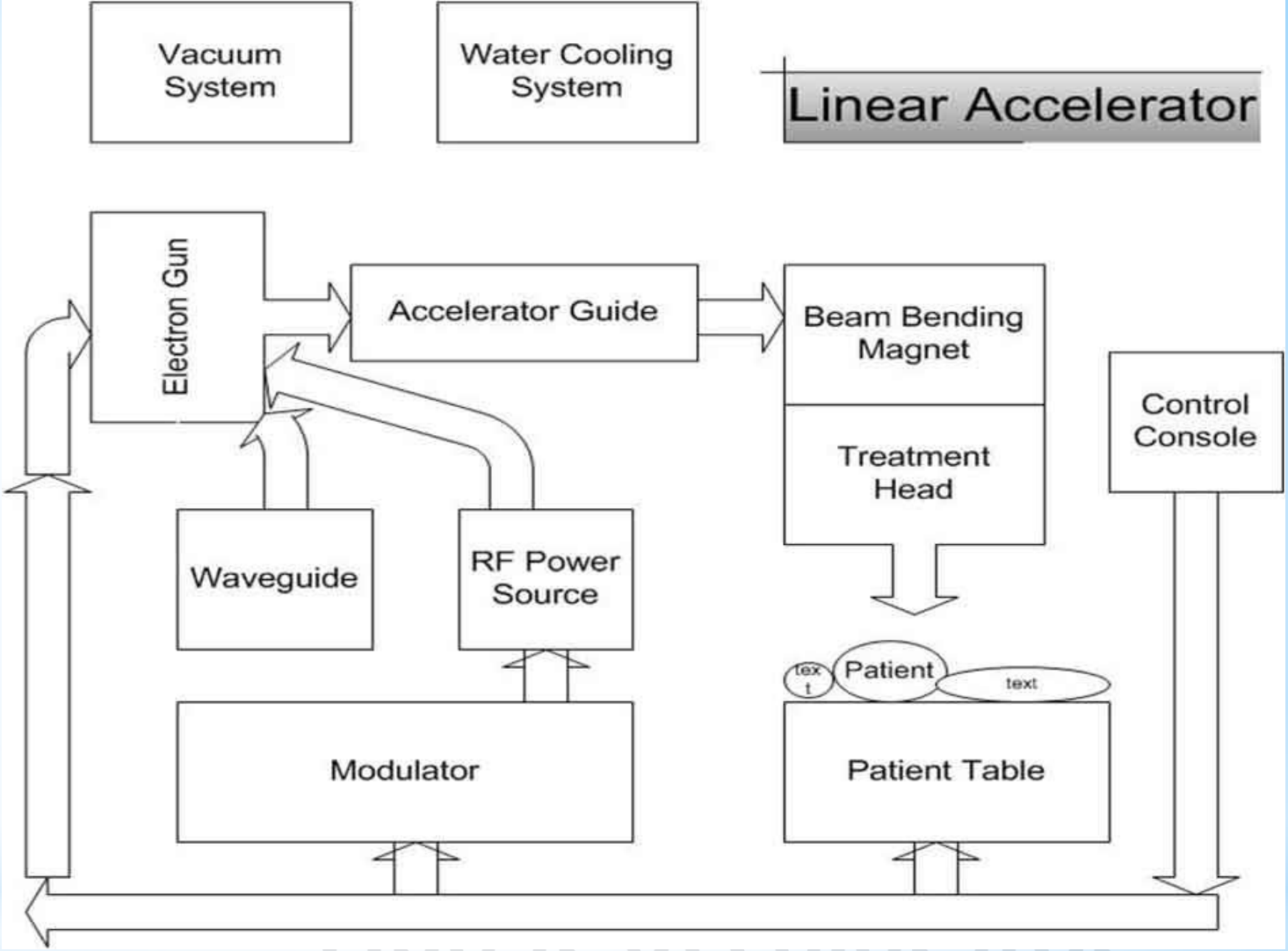
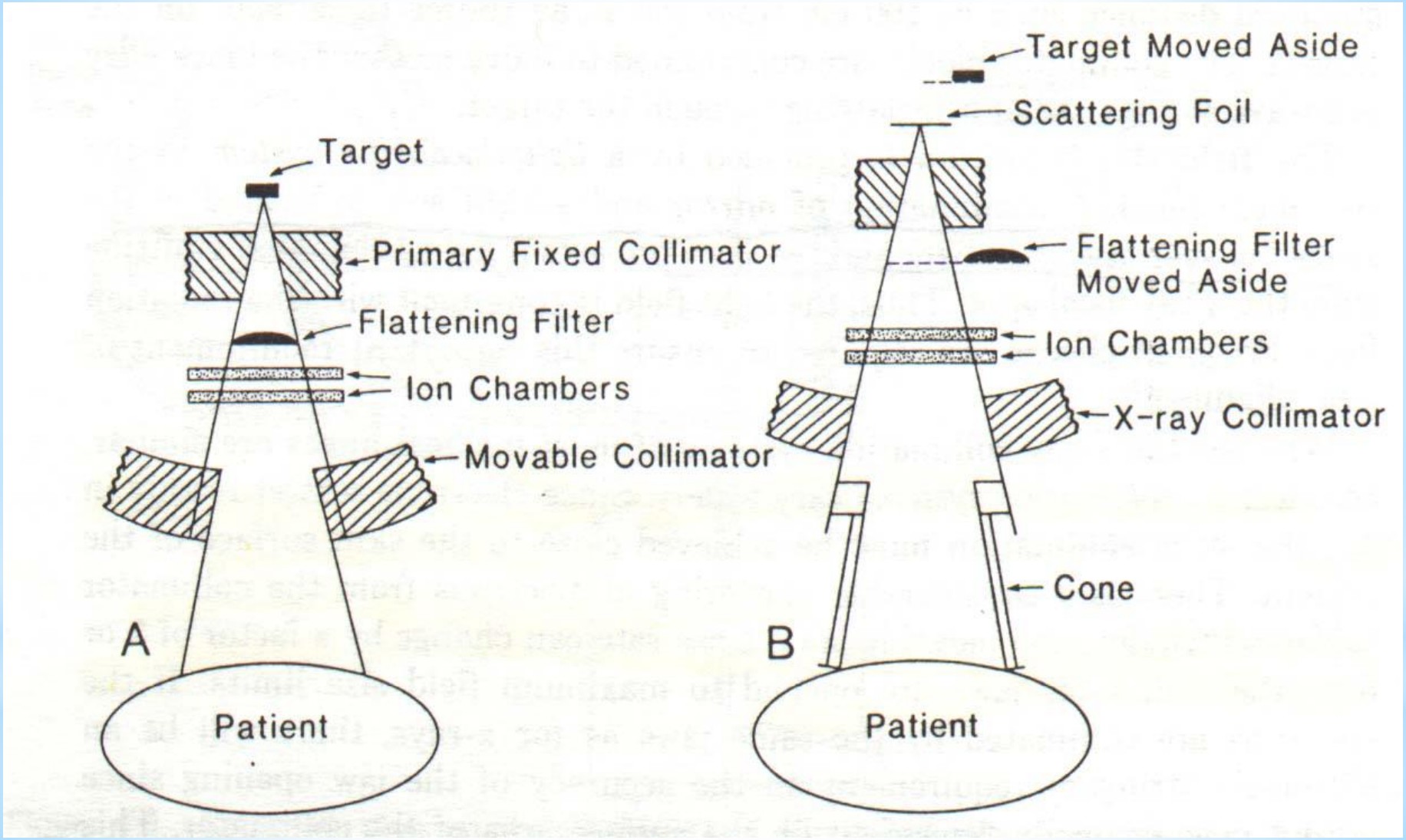


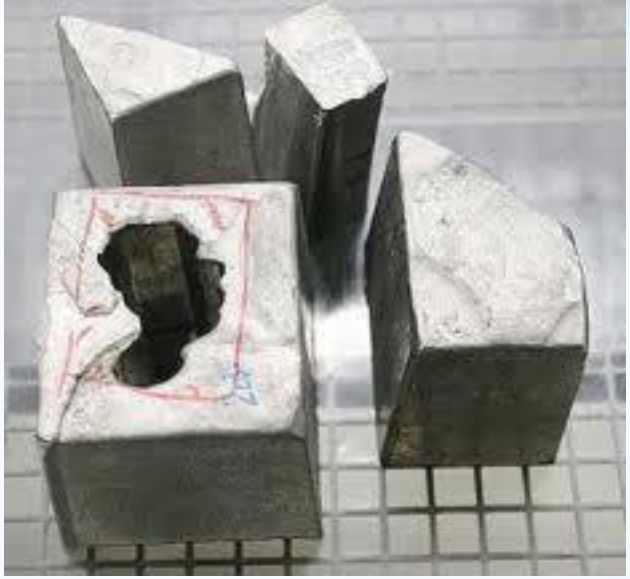
Figure 4. A model of the 1953 8 MeV linac installation at Hammersmith Hospital.

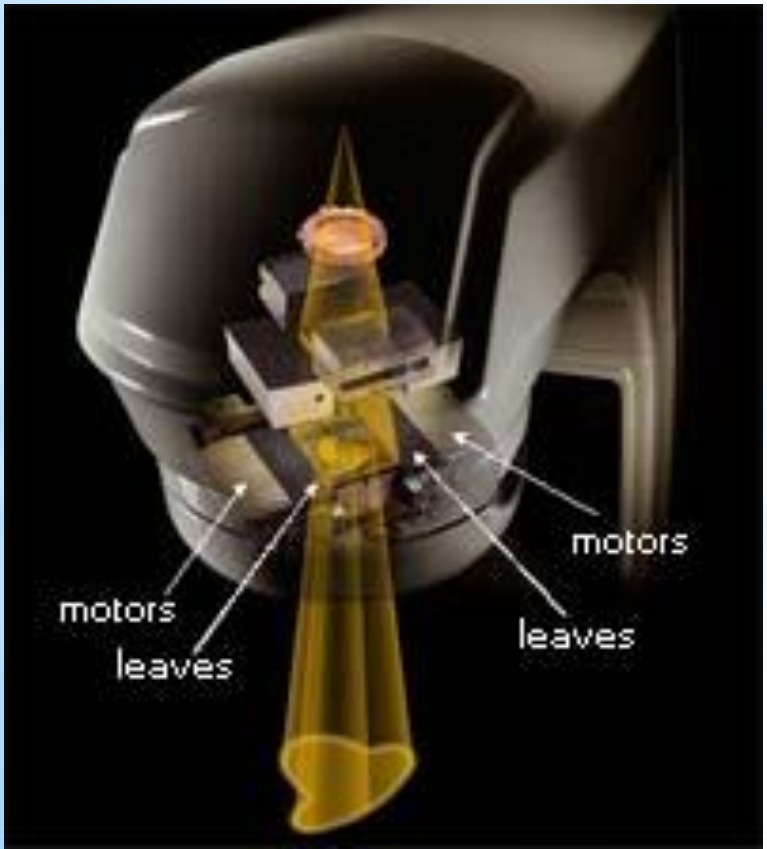
Figure 8. A 6 MeV MEL linac at Cookridge Hospital, Leeds, mid-1960s.

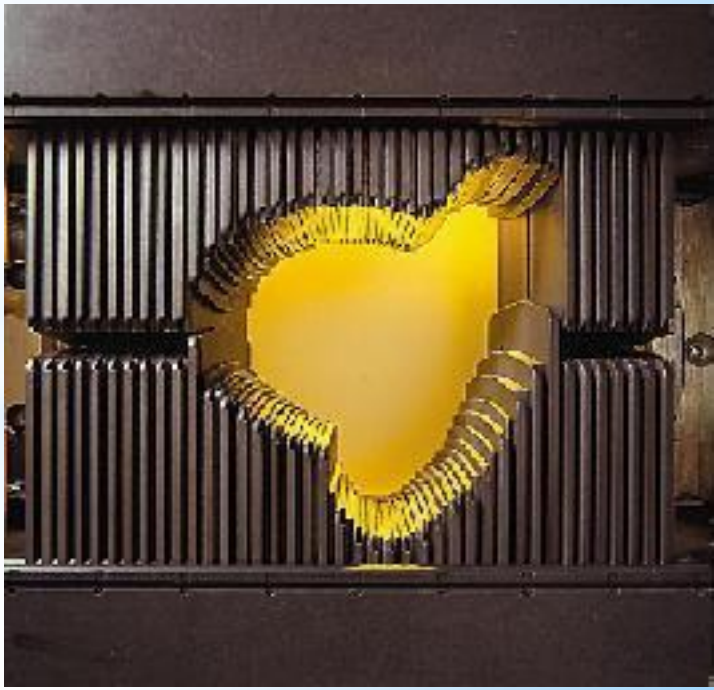


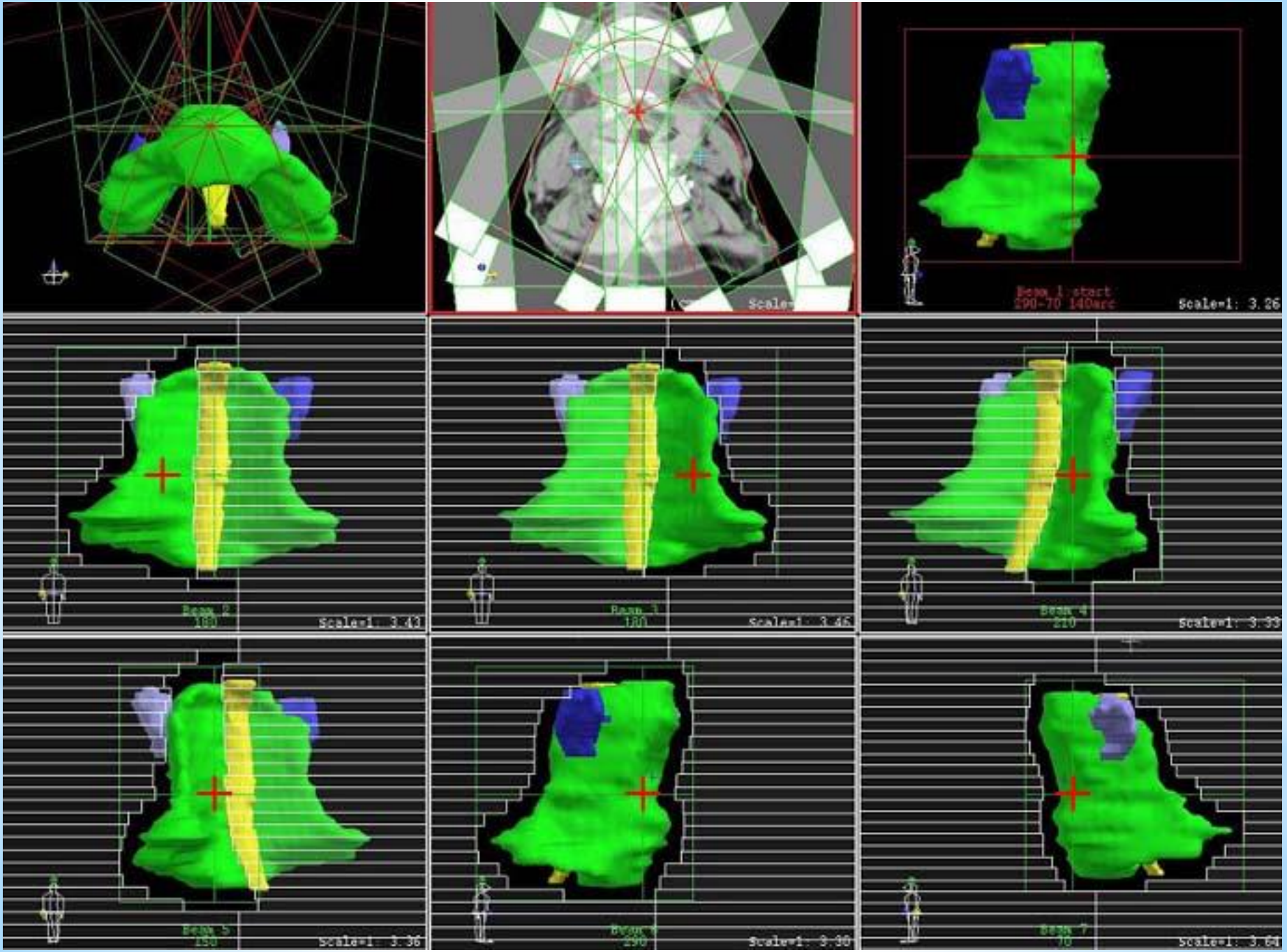
Modern linacs:
changed in technology: beam generation and beam collimation
Increased beam energy: 6-10-15-18-21 MV
Real time imaging: CBCT


Target
Primary Fixed Collimator
Flattening Filter
Ion Chambers
Movable Collimator
A
Patient
Target Moved Aside
Scattering Foil
Flattening Filter
Moved Aside
Ion Chambers
X-ray Collimator
Cone
B
Patient




motors
motors
leaves
leaves

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290-70 140arc
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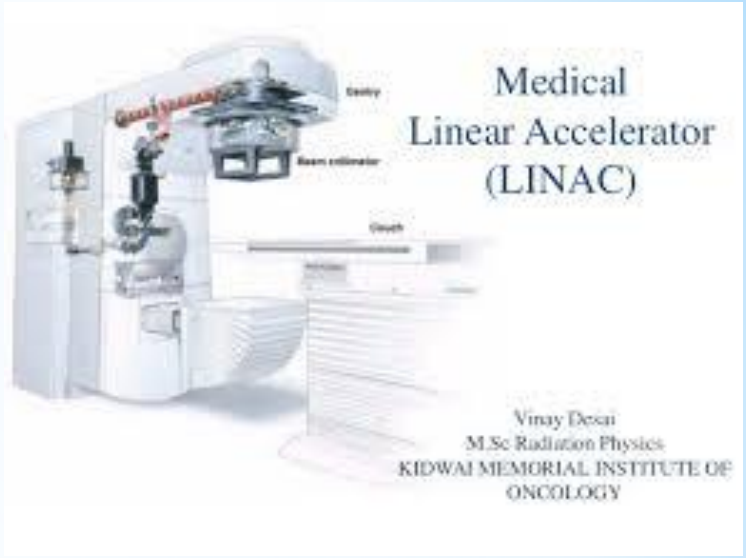
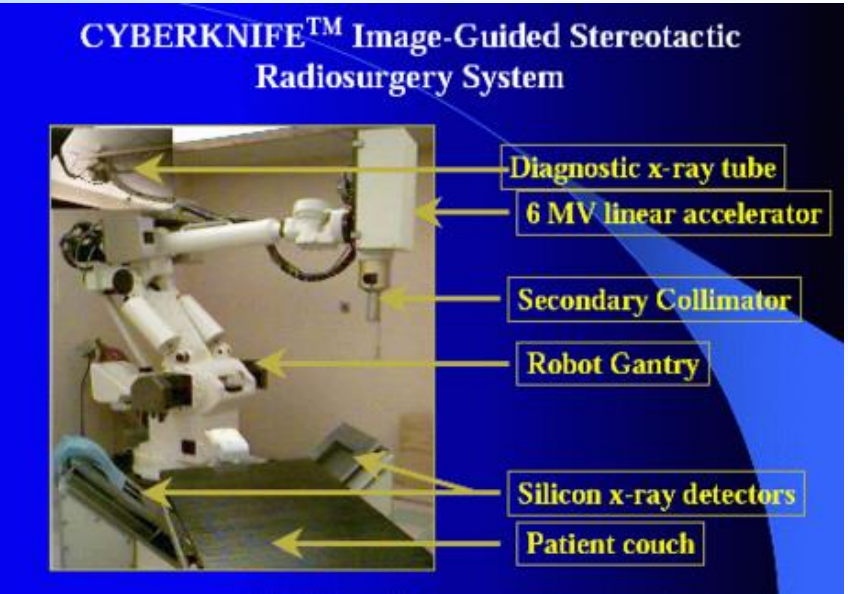
Beam 2
180
Scale=1: 3.43
Beam 3
180
Scale=1: 3.46
Beam 4
220
Scale=1: 3.33
Beam 5
250
Scale=1: 3.36
Beam 6
290
Scale=1: 3.30
Beam 7
70
Scale=1: 3.64

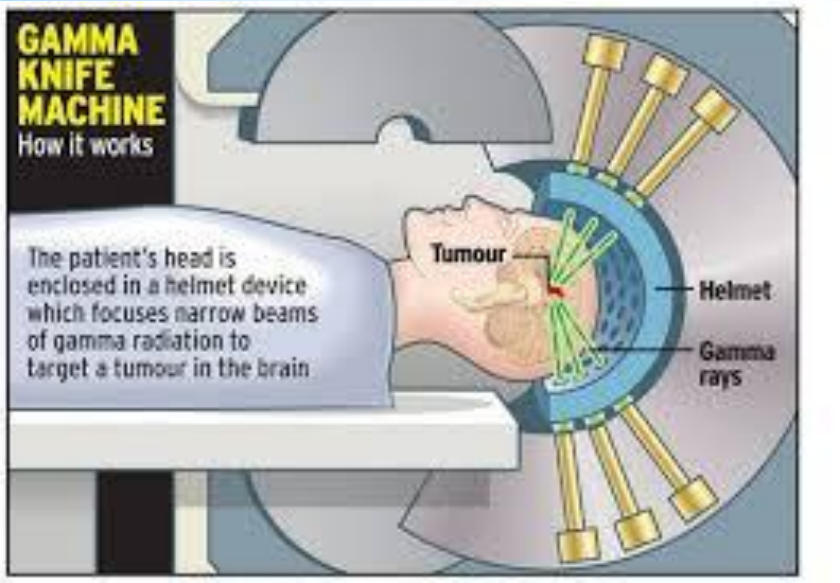

Medical
Linear Accelerator
(LINAC)
Vinay Desai
M.Sc Radiation Physics
KIDWAI MEMORIAL INSTITUTE OF
ONCOLOGY


VARIAN

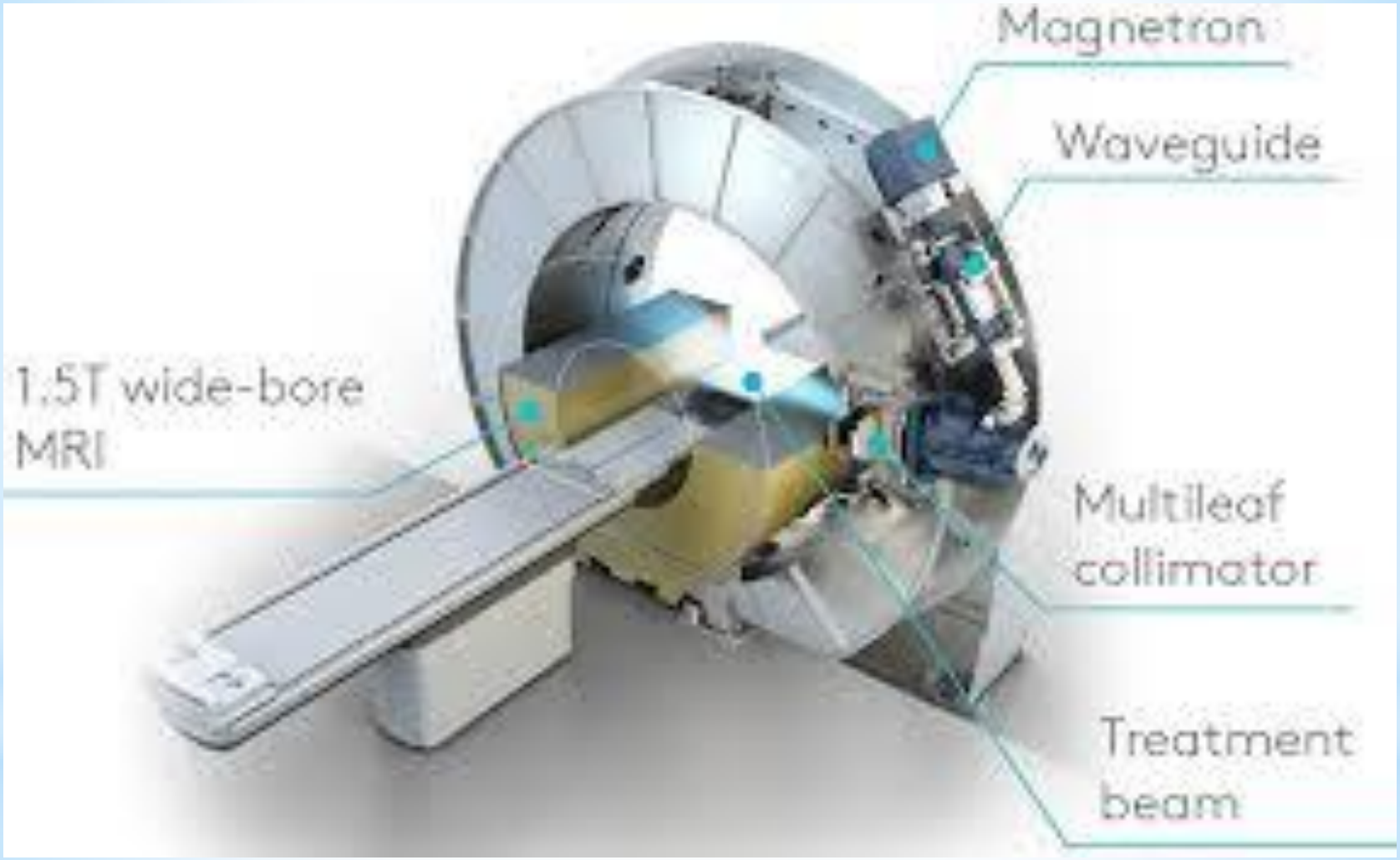

Gantry
kV panel
Phantom
6D motion couch
Information screen
kV X-ray tube
MV EPID panel
AXESSE

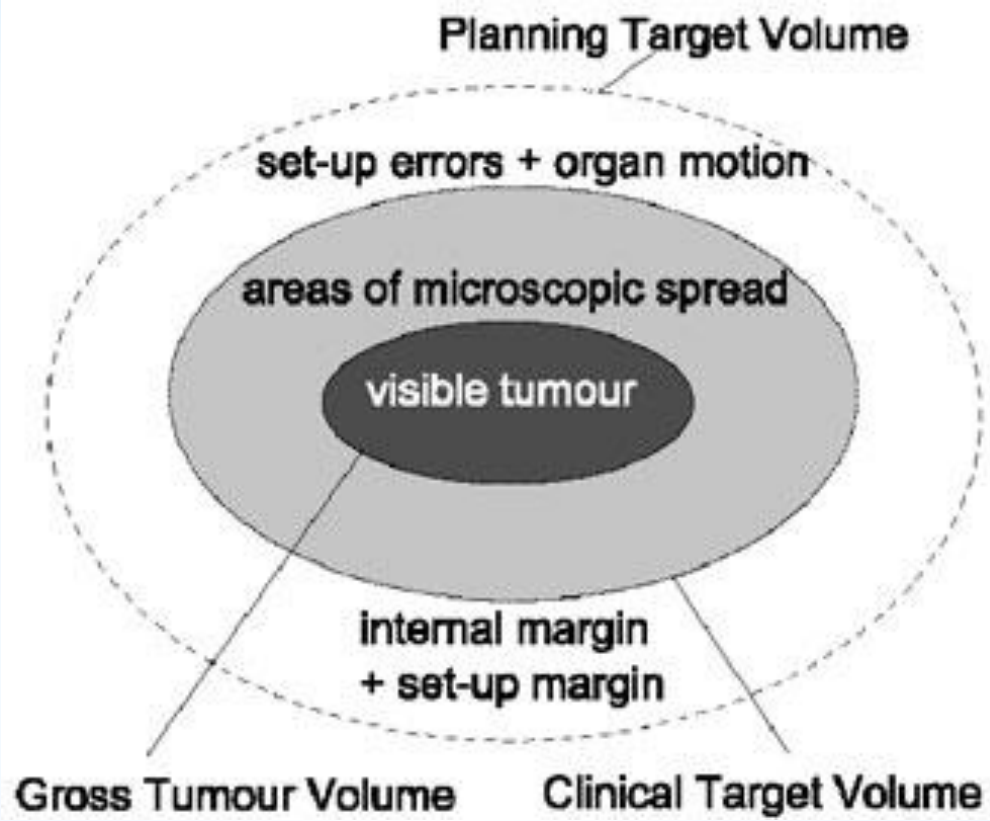
All high level radiosurgery linear accelerators (Novalis Tx, Axesse, TrueBeam and CyberKnife…) and cobalt machines (Gamma Knife) are both robotic and image guided.





201 cobalt-60 sources


Magnetron
Waveguide
1.5T wide-bore
MRI
Multileaf
collimator
Treatment
beam



*XRT Treatment Volumes

* Treatment Sequence

Patient referral to oncology		
Investigations	History, physical examination, imaging, biopsy, pathology	
Cancer staging	T = tumor size N = lymph node extension M = metastasis	
Multidisciplinary Tumor Board	Surgeon, radiation oncologist, medical oncologist, pathologist & radiologist	Treatment recommendations / clinical trials
Radiotherapy	CT simulation: immobilisation, isocenter, marking CT planning: image fusion (US/MRI/PET) Target volumes delineation Treatment planning/dosimetry/Physics	

2D

TV: GTV, CTV, PTV

OAR: organs at risk: normal critical structures within the radiation fields that required protection during treatment planning

IGRT

3D conformal radiation therapy is a cancer **treatment** that shapes the **radiation** beams to match the shape of the tumor

The goal of three-dimensional conformal radiotherapy (**3D**-**CRT**) is to deliver a conformal dose distribution to tumors, while sparing surrounding normal structures. The use of patient specific **3D** images in the treatment planning process distinguishes **3D**-**CRT** from conventional radiotherapy.

IMRT

* Intensity-modulated radiation therapy (IMRT) is a type of conformal radiotherapy that uses a linear accelerator to deliver an advanced type of high-precision radiotherapy that shapes the radiation beam to closely fit the area of the tumour. The linear accelerator has a device called a multileaf collimator which is made up of thin leaves which move independently and form shapes that fit precisely around the treatment area. This means that the tumour receives a high dose and normal healthy cells nearby receive a much lower dose. IMRT allows the dose to be shaped to the tumour by modulating—or controlling—the intensity of the radiation beam. This allows different doses of radiation to be given across the tumour.

VMAT

Volumetric Modulated Arc Therapy (VMAT) is a new type of IMRT. The linear accelerator rotates around the patient during treatment. The machine continuously reshapes and changes the intensity of the radiation beam as it moves around the body. Giving the radiotherapy in this way makes it very accurate, shortens the treatment time, and uses a lower overall dose of radiation.

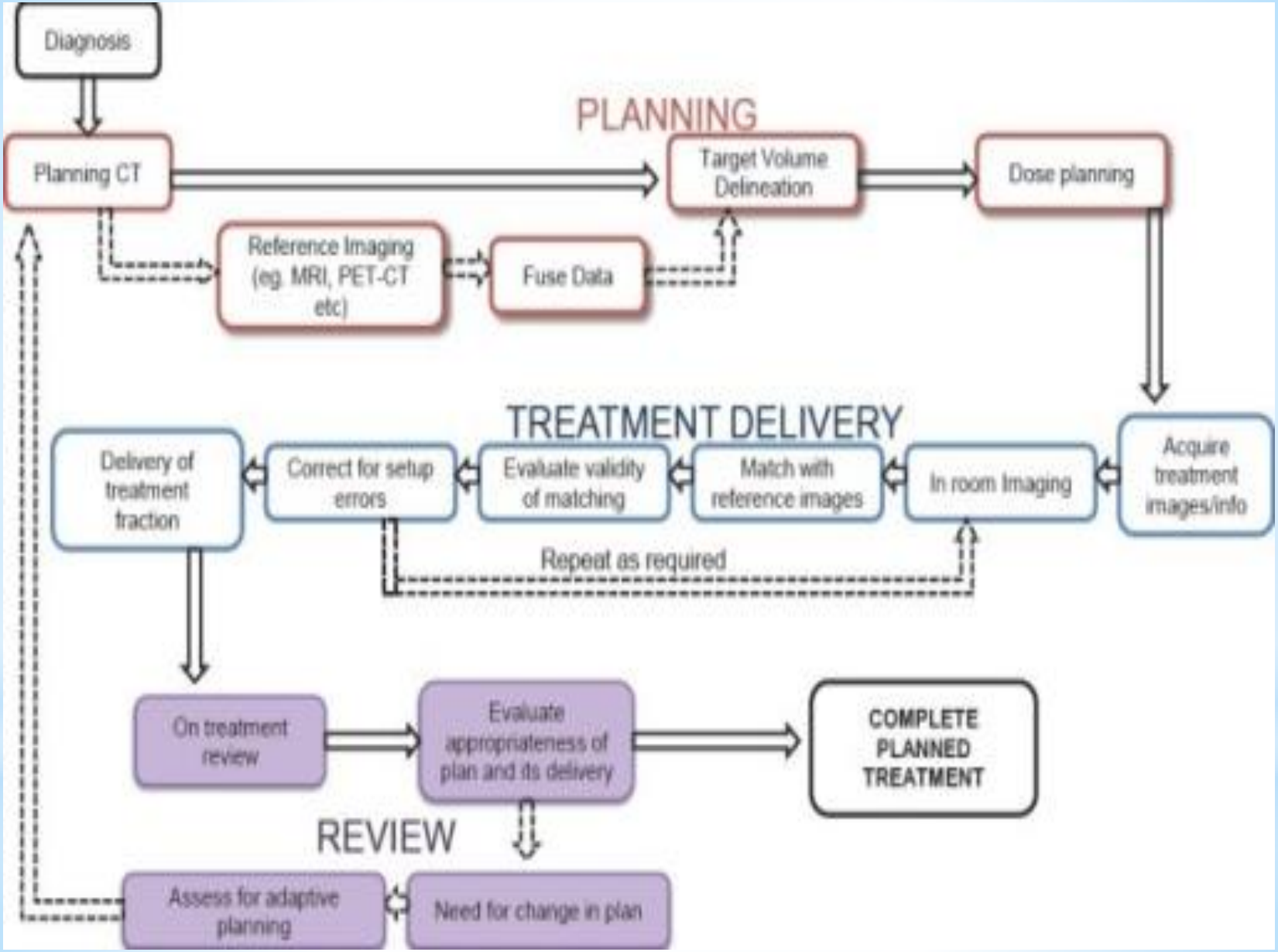
DVH

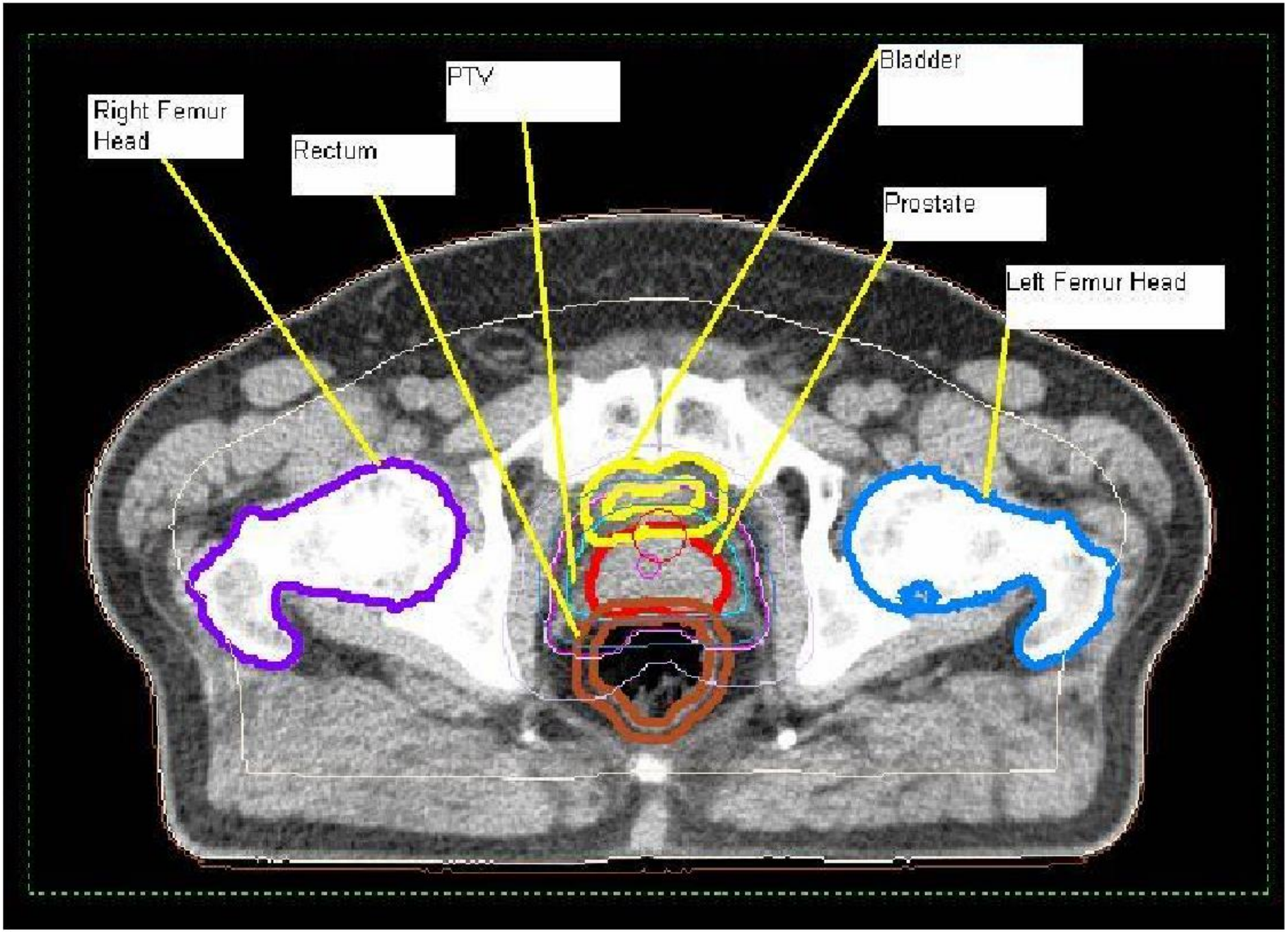
*EBRT

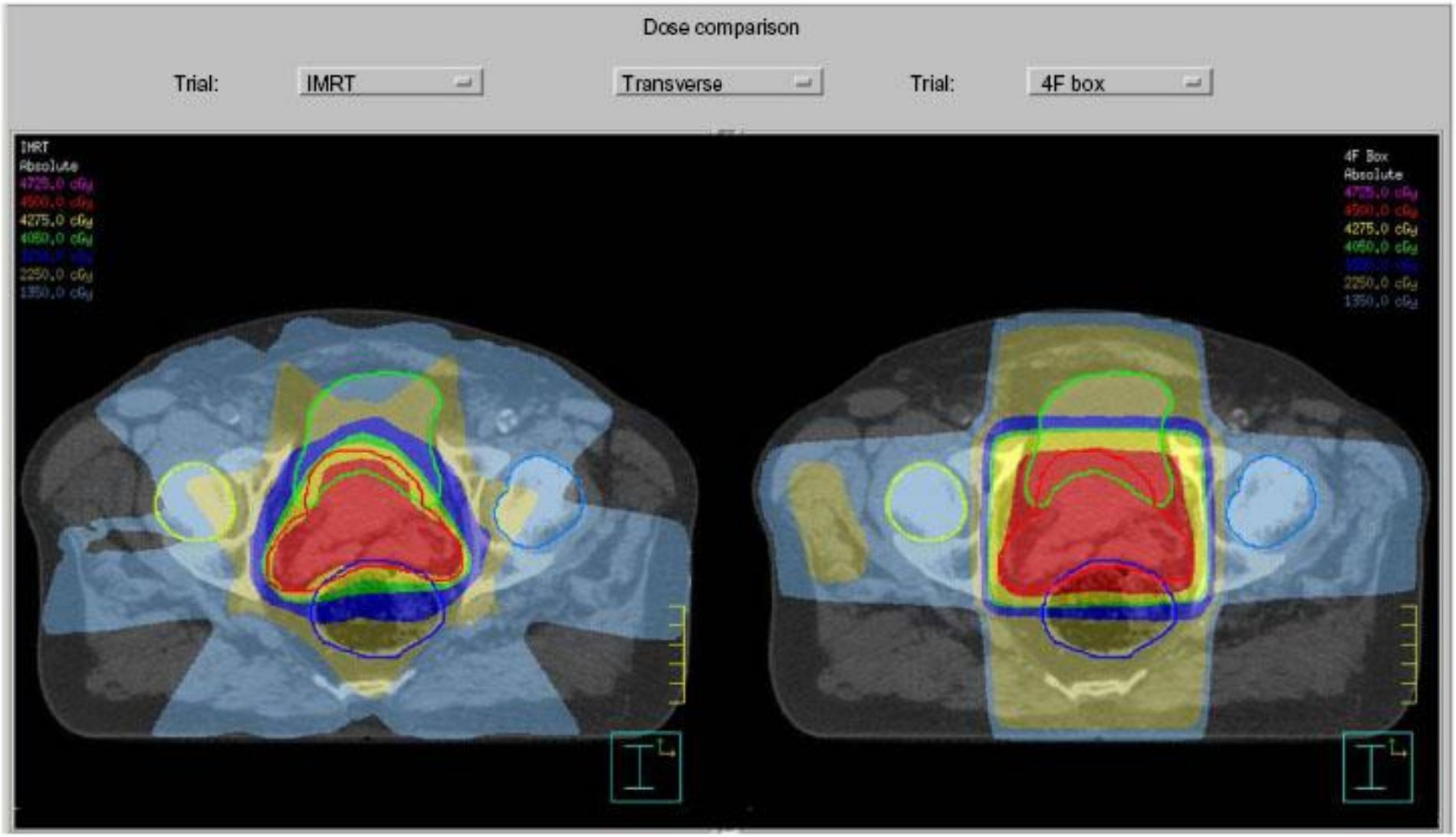
IGRT

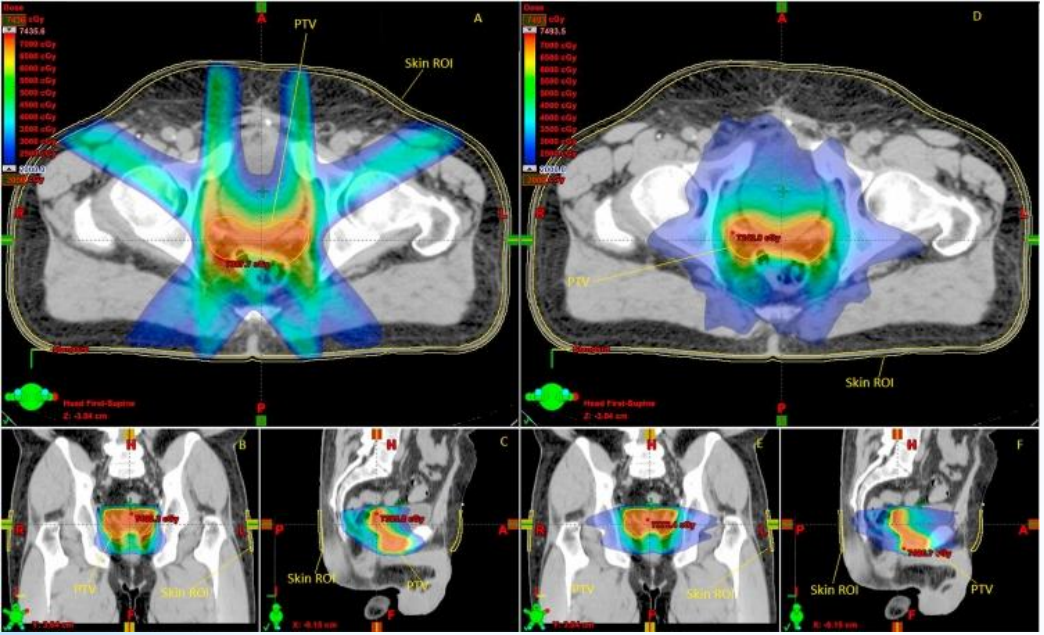
A Physician's Perspective

- A long overdue technology
- Known for years that….
  - Patients are difficult to setup
  - Targets change in position between (inter-fraction) and during (intra-fraction) treatments
  - Tumors and patients change over the treatment course
- Increasingly aware that such factors effect the quality and delivery of treatment


Diagnosis
PLANNING
Planning CT
Target Volume Delineation
Dose planning
Reference Imaging (eg. MRI, PET-CT etc)
Fuse Data
TREATMENT DELIVERY
Delivery of treatment fraction
Correct for setup errors
Evaluate validity of matching
Match with reference images
In room Imaging
Acquire treatment images/info
Repeat as required
On treatment review
Evaluate appropriateness of plan and its delivery
COMPLETE PLANNED TREATMENT
REVIEW
Assess for adaptive planning
Need for change in plan


Right Femur Head
Rectum
PTV
Bladder
Prostate
Left Femur Head


Dose comparison
Trial:
IMRT
Transverse
Trial:
4F box
IMRT
Absolute
4275.0 cGy
2250.0 cGy
1350.0 cGy
4F Box
Absolute
4275.0 cGy
2250.0 cGy
1350.0 cGy



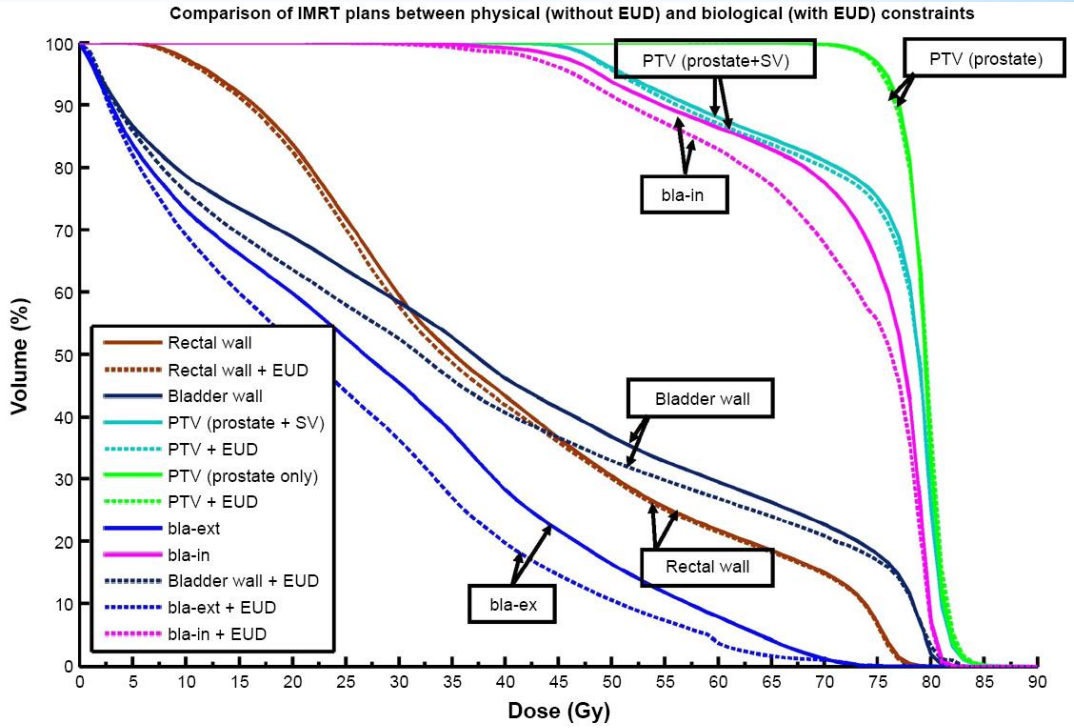
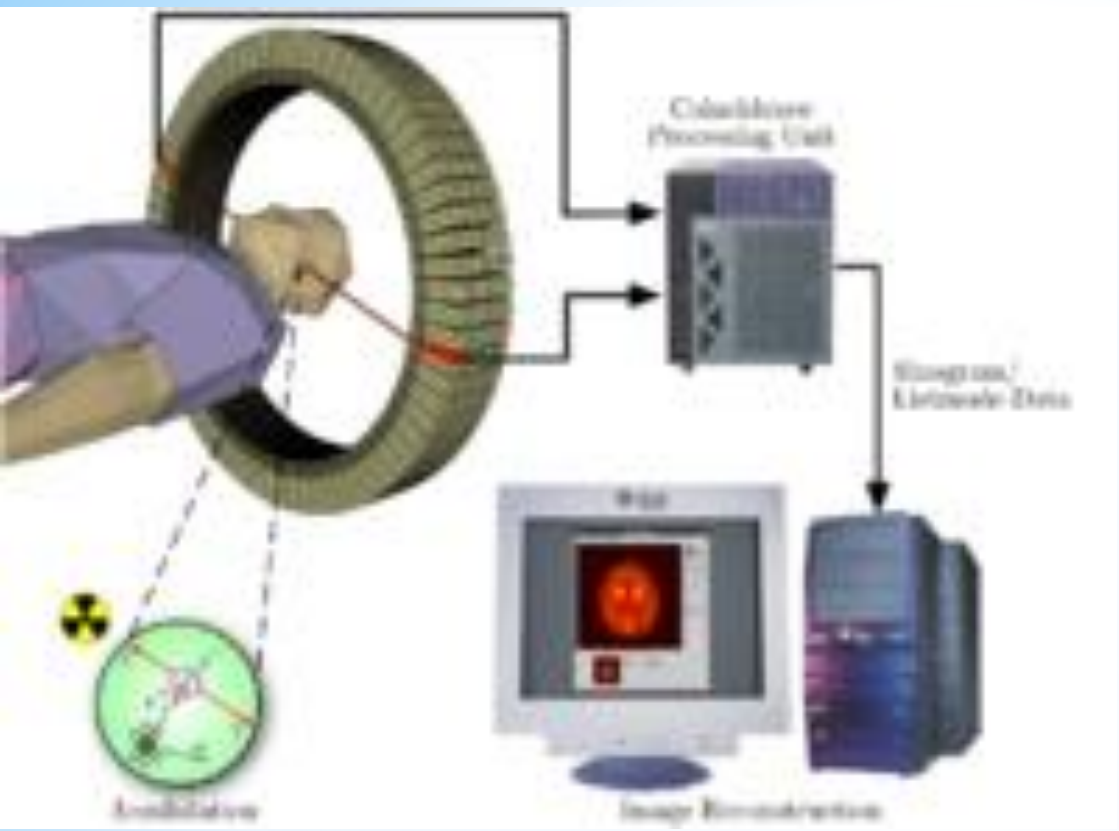


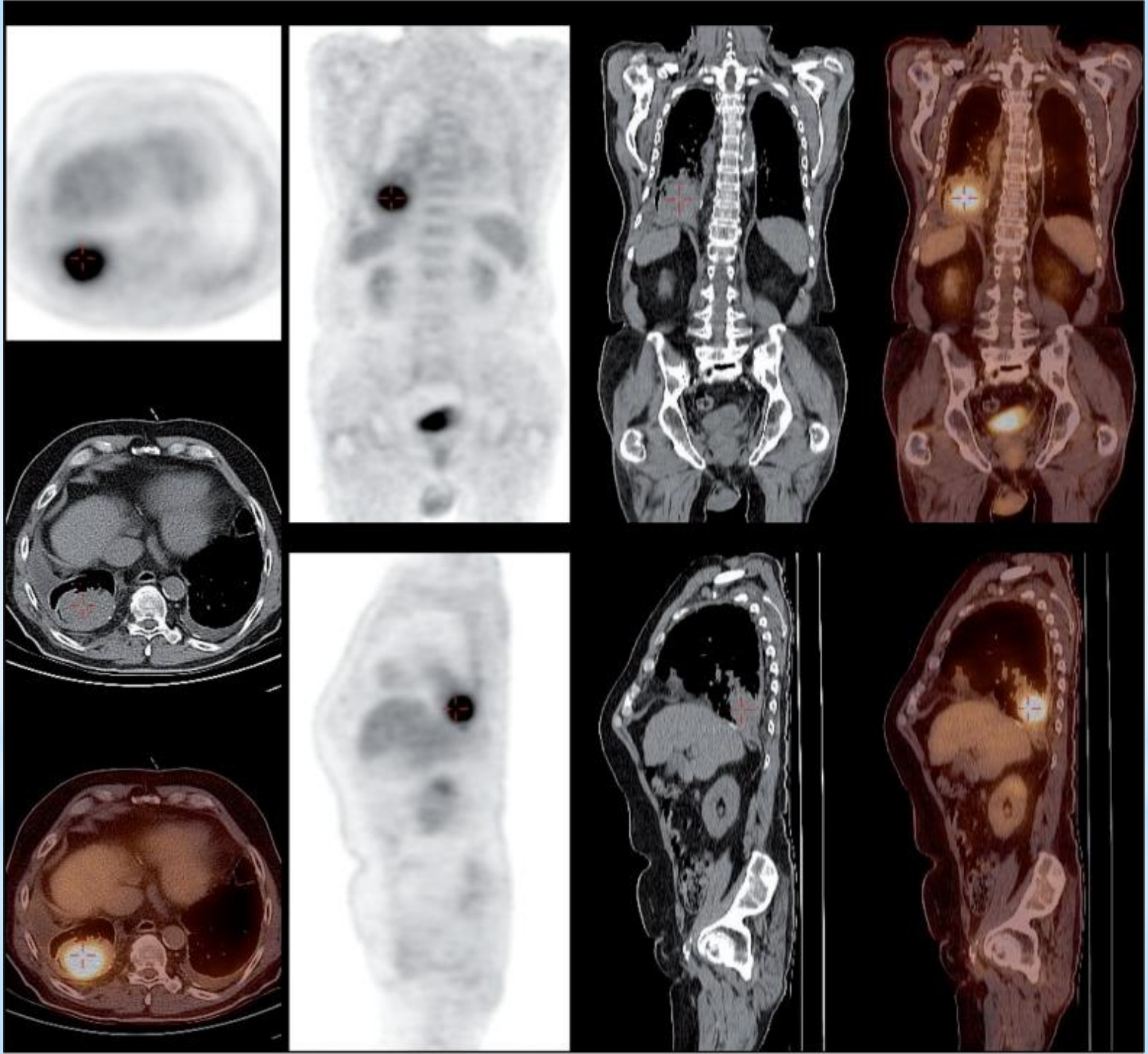
Figure 2 Mean DVH of the physical plan and biological EUD plan.
Abbreviations: IMRT, intensity-modulated radiotherapy; bla-in, internal-bladder wall; bla-ex, external-bladder wall; DVH, dose–volume histograms; SV, seminal vesicles; EUD, equivalent uniform dose; PTV, planning target volume.

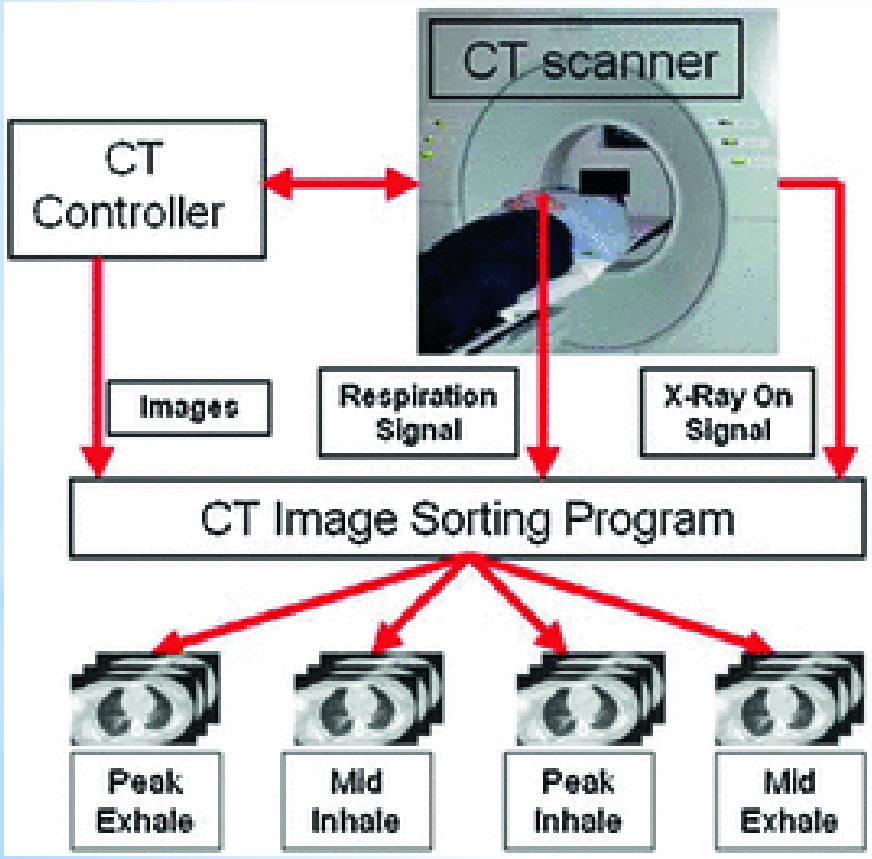


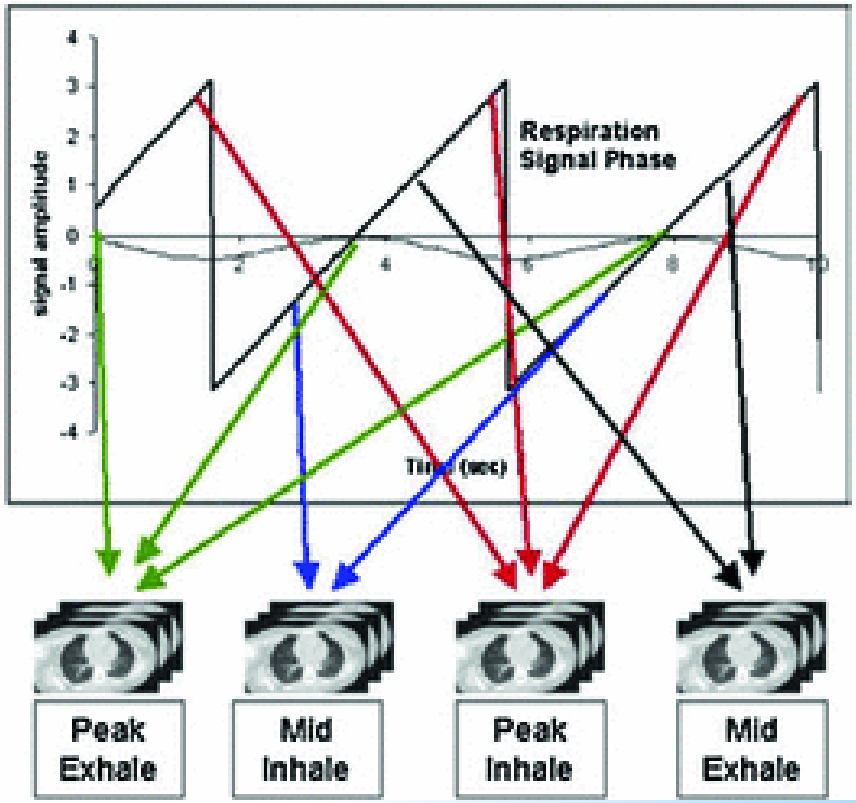
Positron emission tomography.
Positron-emission tomography (**PET**) is a nuclear medicine functional imaging technique that is used to observe metabolic processes in the body as an aid to the diagnosis of disease.

The uptake of ^{18}F-FDG by tissues is a marker for the tissue uptake of glucose, which in turn is closely correlated with certain types of tissue metabolism. After ^{18}F-FDG is injected into a patient, a PET scanner can form two-dimensional or three-dimensional images of the distribution of ^{18}F-FDG within the body.

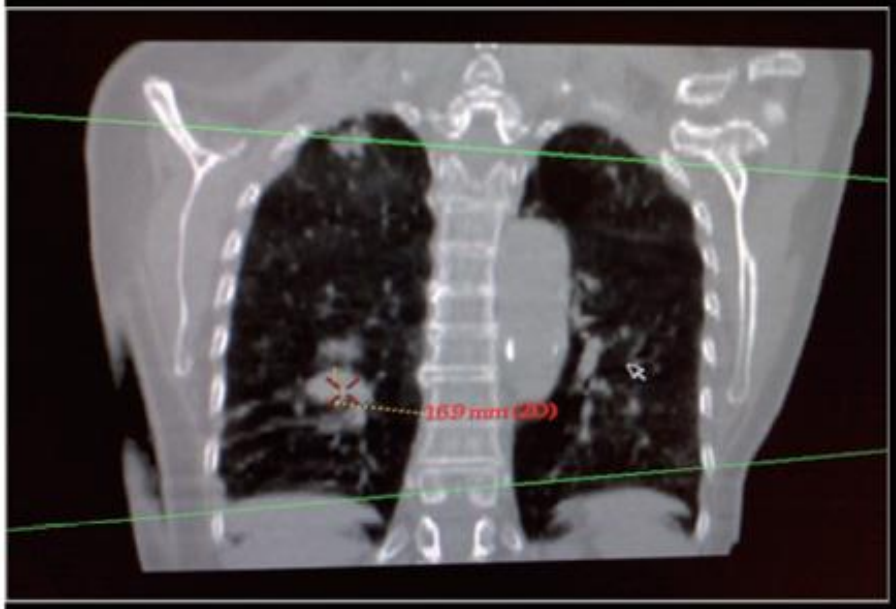
Other tracers:
18-FLT
FMISO
Choline
PSMA…



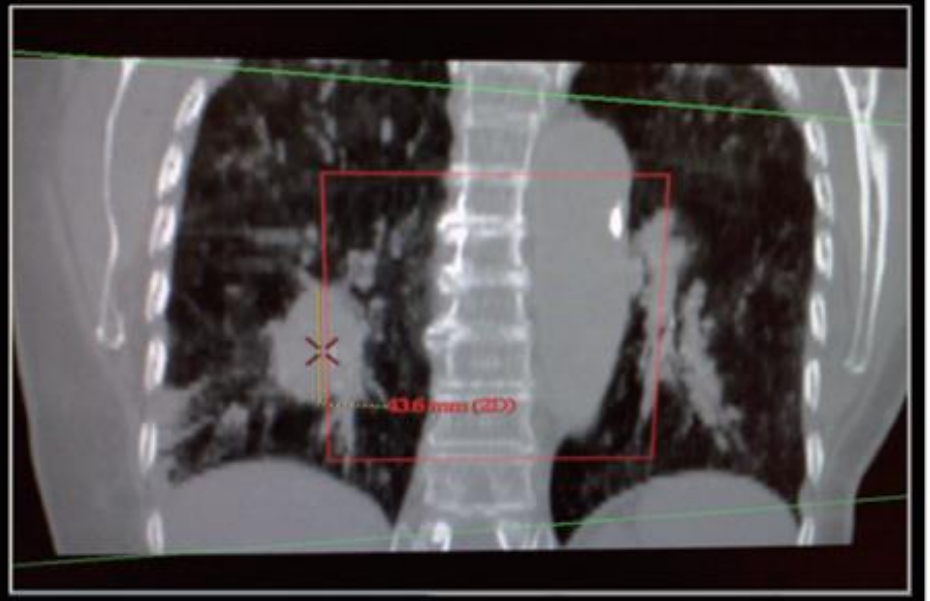

CT scanner
CT Controller
Images
Respiration Signal
X-Ray On Signal
CT Image Sorting Program
Peak Exhale
Mid Inhale
Peak Inhale
Mid Exhale


Respiration Signal Phase
signal amplitude
Peak Exhale
Mid Inhale
Peak Inhale
Mid Exhale

Gross Tumor Volume (GTV) defined by Conventional CT (Free Breathing)



Internal Target Volume (ITV) defined by 4 dimensional CT (10 Phases Combined)



4D CT Simulator

The trace of the target motion allow the creation of a internal target volume (ITV) for treatment planning

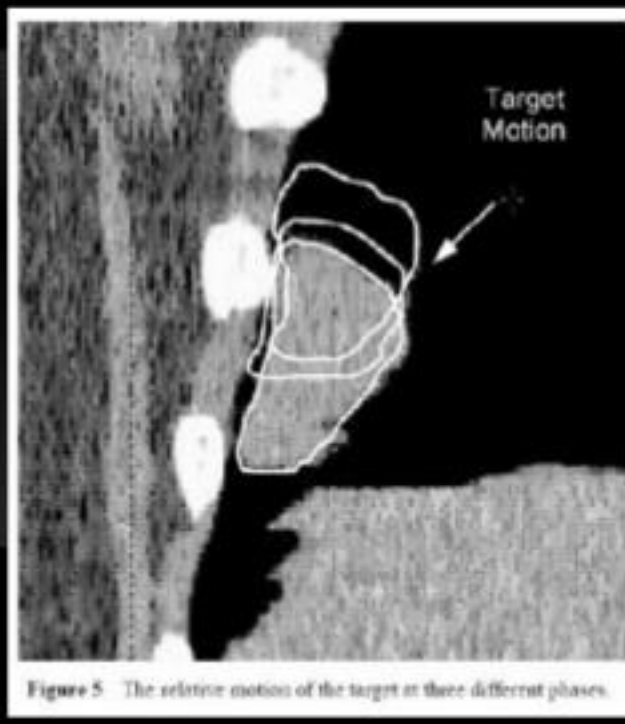
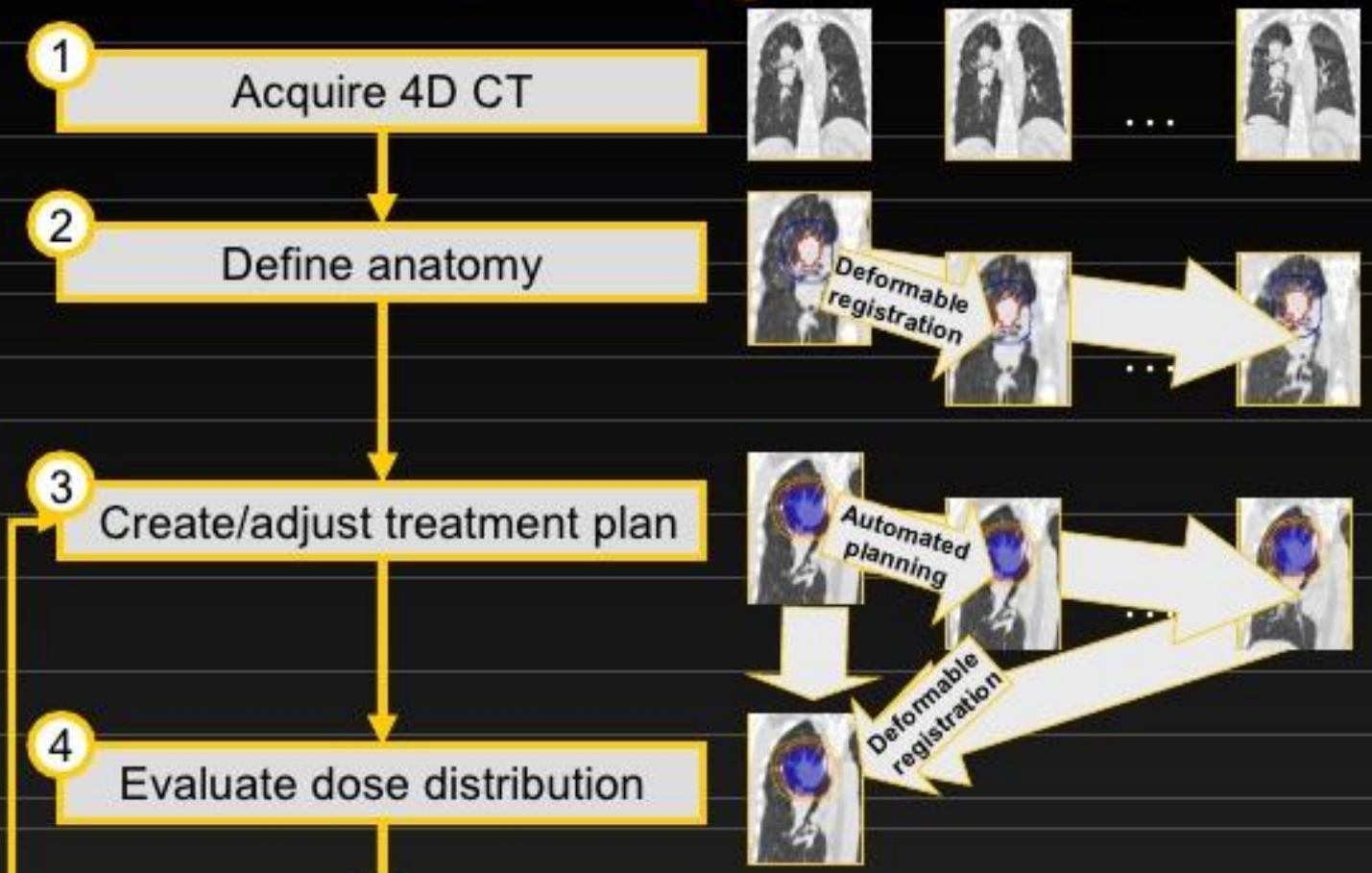
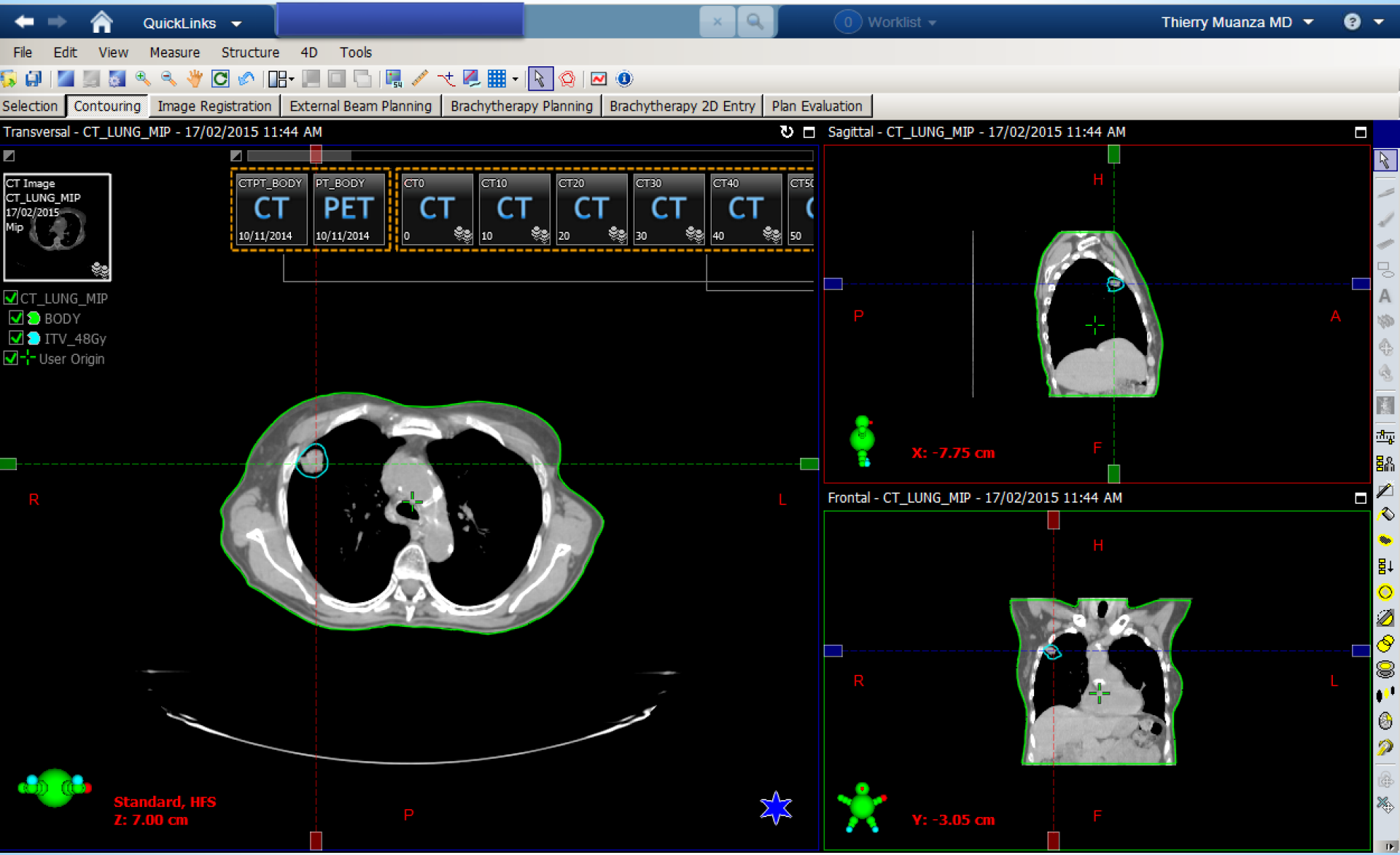


Figure 5 The relative motion of the target at three different phases.

4D Planning Flow Chart




QuickLinks
Worklist
Thierry Muanza MD
File
Edit
View
Measure
Structure
4D
Tools
Selection
Contouring
Image Registration
External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
Transversal - CT_LUNG_MIP - 17/02/2015 11:44 AM
Sagittal - CT_LUNG_MIP - 17/02/2015 11:44 AM
Frontal - CT_LUNG_MIP - 17/02/2015 11:44 AM
CT Image
CT_LUNG_MIP
17/02/2015
Mip
CTPT_BODY
PT_BODY
CT0
CT10
CT20
CT30
CT40
CT
PET
10/11/2014
CT_LUNG_MIP
BODY
ITV_48Gy
User Origin
R
L
P
H
A
F
X: -7.75 cm
Standard, HFS
Z: 7.00 cm
Y: -3.05 cm


QuickLinks
Worklist
Thierry Muanza MD
File
Edit
View
Measure
Structure
4D
Tools
Selection
Contouring
Image Registration
External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
Transversal - CT80 - CT_LUNG_MIP - 17/02/2015 11:44 AM
FEB 17 2015
CT Image
CT80
14/04/2015
80
CT Image
CT_LUNG_MIP
17/02/2015
Mip
CT20
CT30
CT40
CT50
CT60
CT70
CT80
CT80
BODY
User Origin
CT_LUNG_MIP
BODY
ITV_48Gy
R
L
P
Standard, HFS
Z: 31.59 cm
0 %
Sagittal - CT80 - CT_LUNG_MIP - 17/02/2015 11:44 AM
H
P
A
F
X: -9.03 cm
0 %
Frontal - CT80 - CT_LUNG_MIP - 17/02/2015 11:44 AM
H
R
L
F
Y: -2.98 cm
0 %


QuickLinks
Worklist
Thierry Muanza MD
File
Edit
View
Measure
Structure
4D
Tools
Selection
Contouring
Image Registration
External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
Transversal - CT80 - CT_LUNG_MIP - 17/02/2015 11:44 AM
FEB 17 2015
CT Image
CT80
14/04/2015
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CT Image
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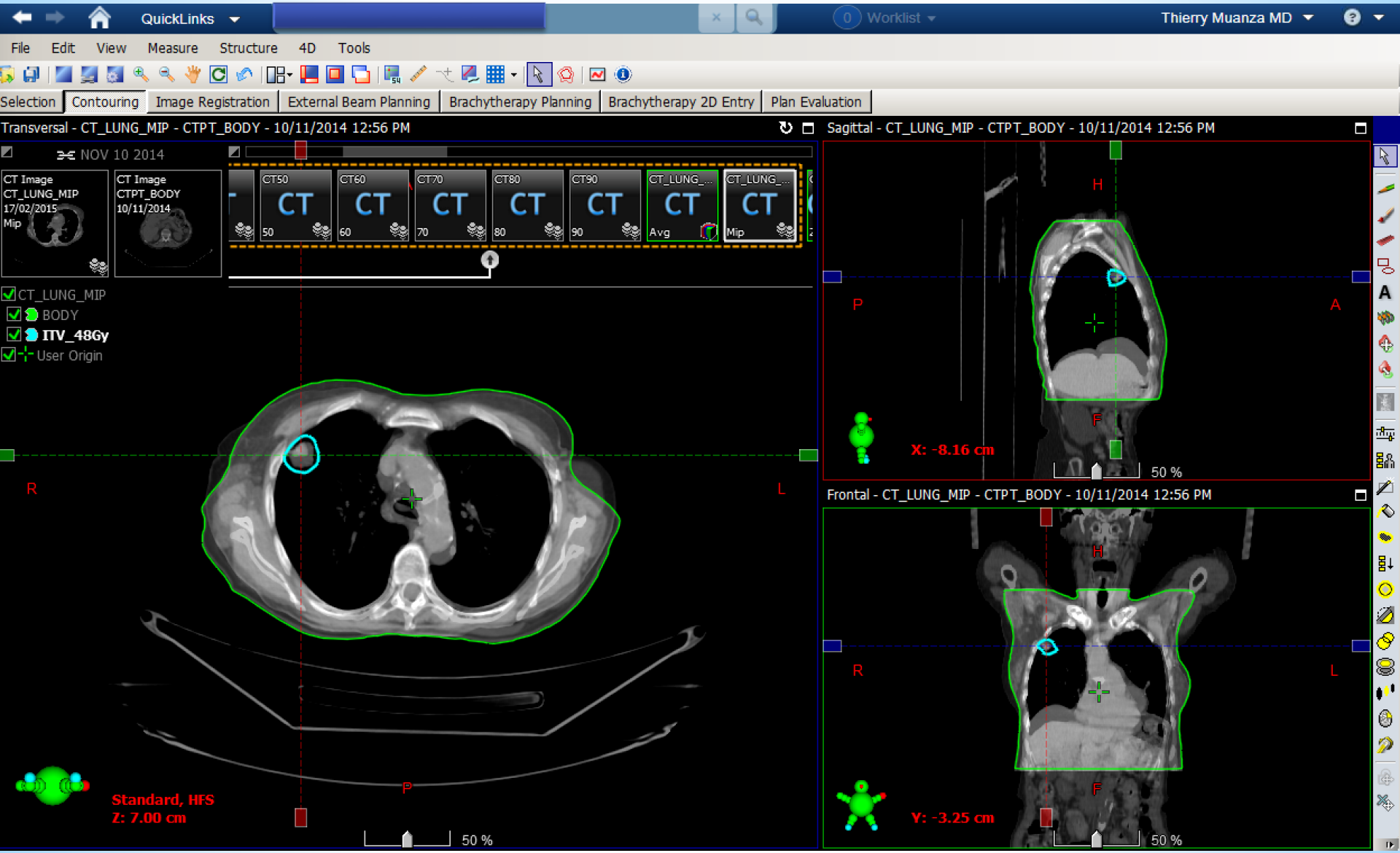
17/02/2015
Mip
CT20
CT30
CT40
CT50
CT60
CT70
CT80
CT80
BODY
User Origin
CT_LUNG_MIP
BODY
ITV_48Gy
R
L
P
Standard, HFS
Z: 31.59 cm
50 %
Sagittal - CT80 - CT_LUNG_MIP - 17/02/2015 11:44 AM
H
P
A
F
X: -9.03 cm
50 %
Frontal - CT80 - CT_LUNG_MIP - 17/02/2015 11:44 AM
H
R
L
F
Y: -2.98 cm
50 %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External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
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NOV 10 2014
CT Image
CT_LUNG_MIP
17/02/2015
Mip
CT Image
CTPT_BODY
10/11/2014
CT50
CT60
CT70
CT80
CT90
CT_LUNG_...
CT_LUNG_...
Avg
Mip
CT_LUNG_MIP
BODY
ITV_48Gy
User Origin
R
L
P
Standard, HFS
Z: 7.00 cm
50 %
Sagittal - CT_LUNG_MIP - CTPT_BODY - 10/11/2014 12:56 PM
H
P
A
F
X: -8.16 cm
50 %
Frontal - CT_LUNG_MIP - CTPT_BODY - 10/11/2014 12:56 PM
H
R
L
F
Y: -3.25 cm
50 %

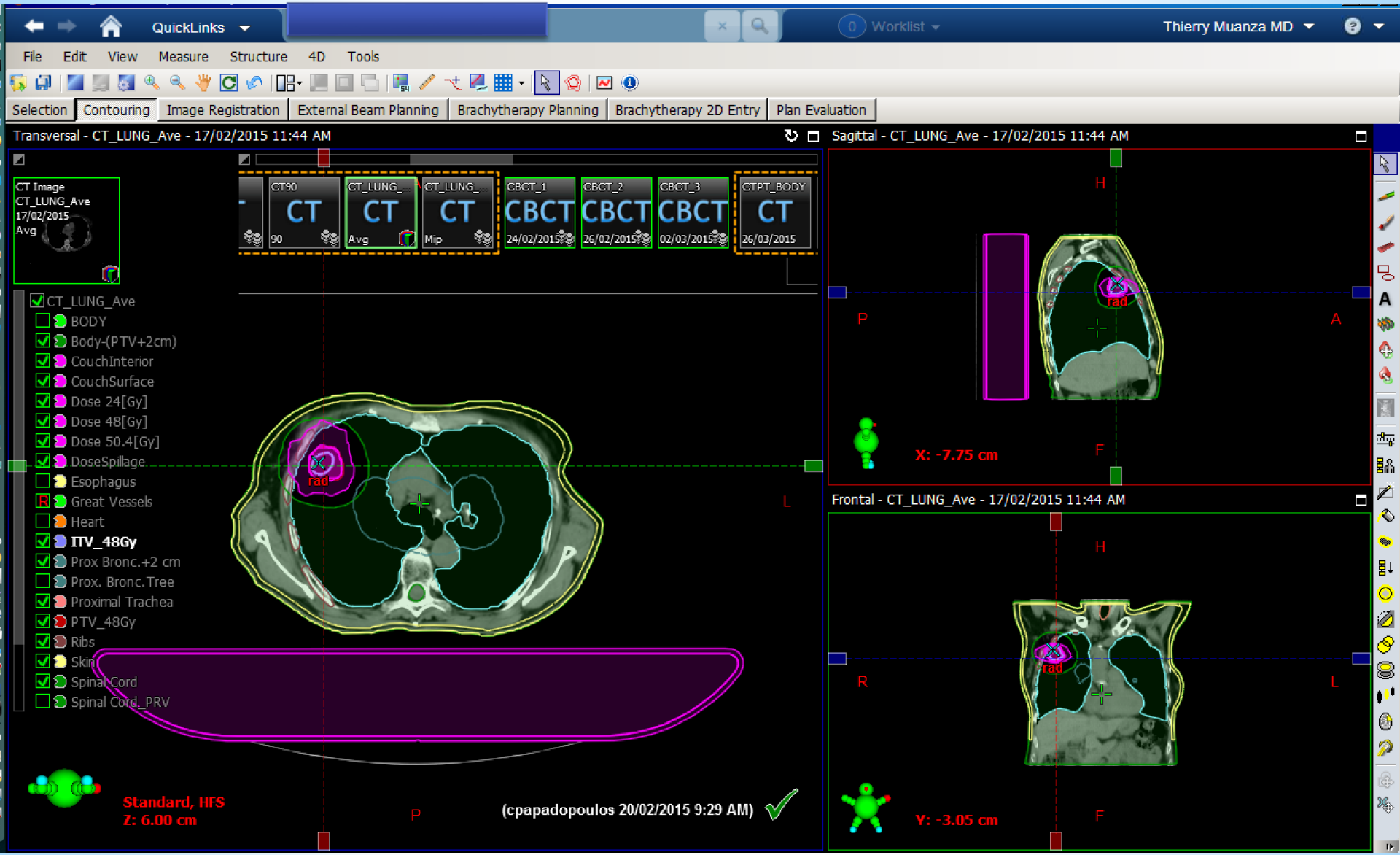
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Image Registration
External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
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Sagittal - CT_LUNG_Ave - 17/02/2015 11:44 AM
Frontal - CT_LUNG_Ave - 17/02/2015 11:44 AM
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CT_LUNG_Ave
17/02/2015
Avg
CT90
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CT_LUNG_...
CBCT_1
CBCT_2
CBCT_3
CTPT_BODY
24/02/2015
26/02/2015
02/03/2015
26/03/2015
CT_LUNG_Ave
BODY
Body-(PTV+2cm)
CouchInterior
CouchSurface
Dose 24[Gy]
Dose 48[Gy]
Dose 50.4[Gy]
DoseSpillage
Esophagus
Great Vessels
Heart
ITV_48Gy
Prox Bronc.+2 cm
Prox. Bronc.Tree
Proximal Trachea
PTV_48Gy
Ribs
Skin
Spinal Cord
Spinal Cord_PRV
rad
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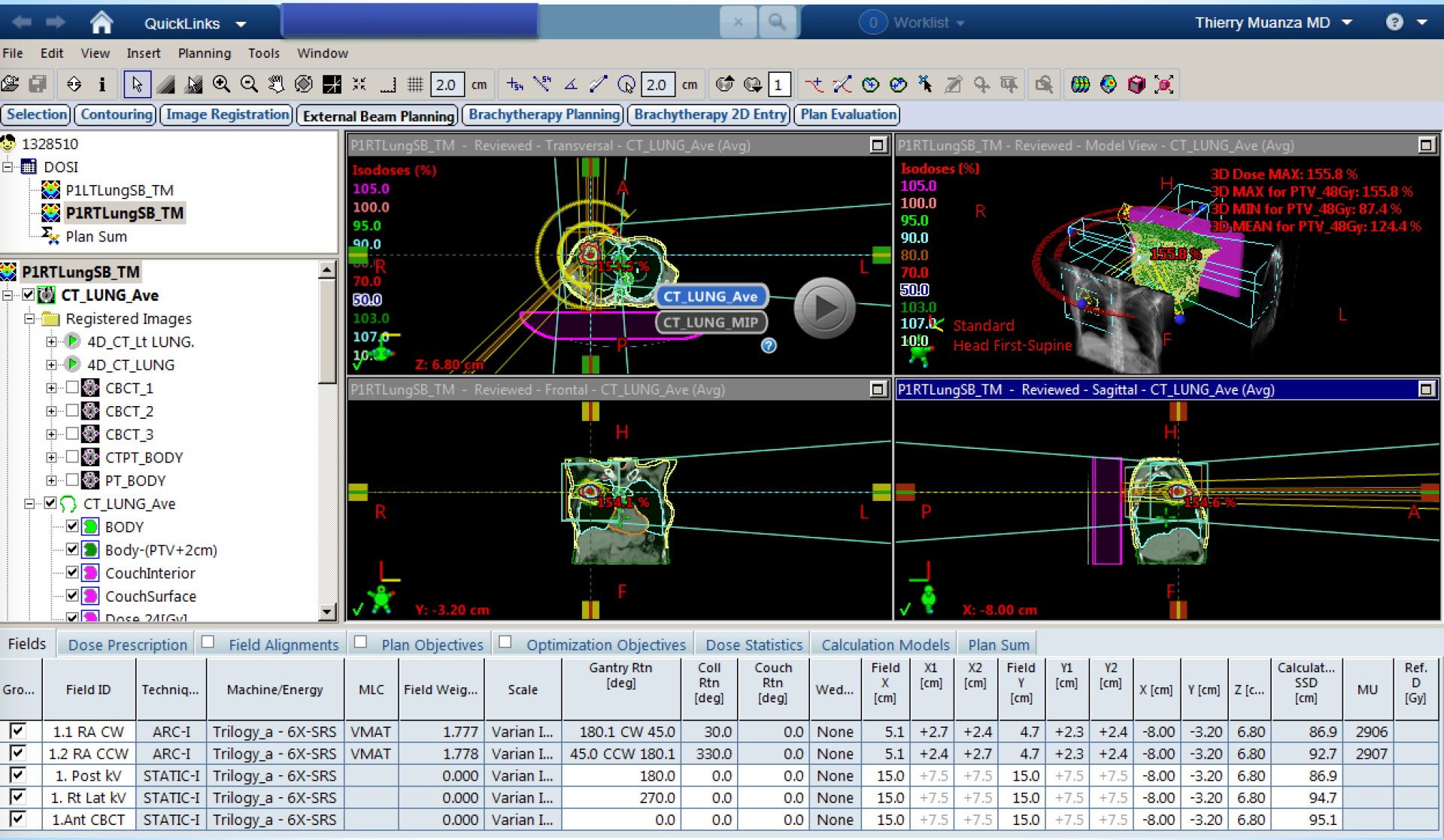
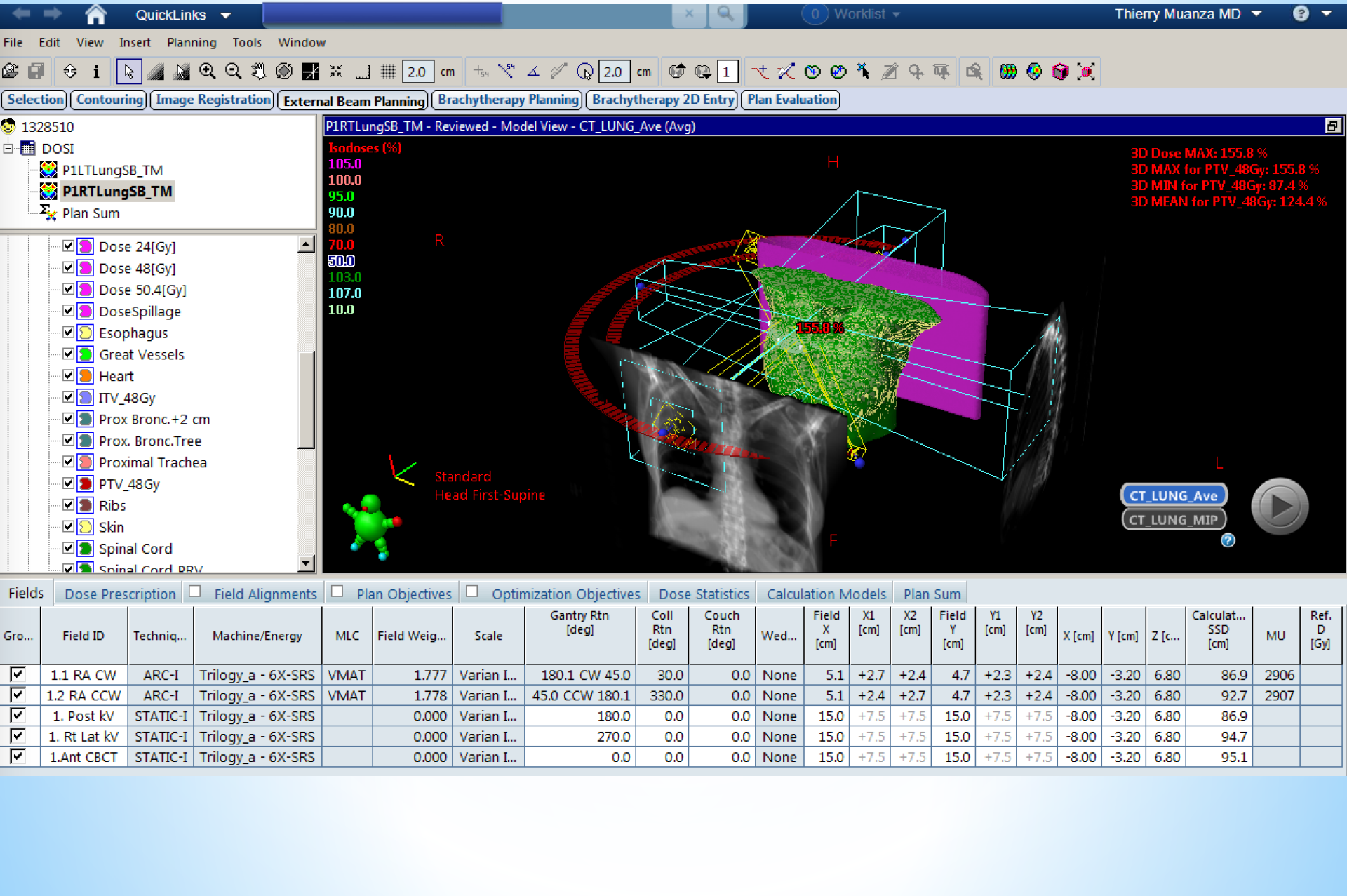
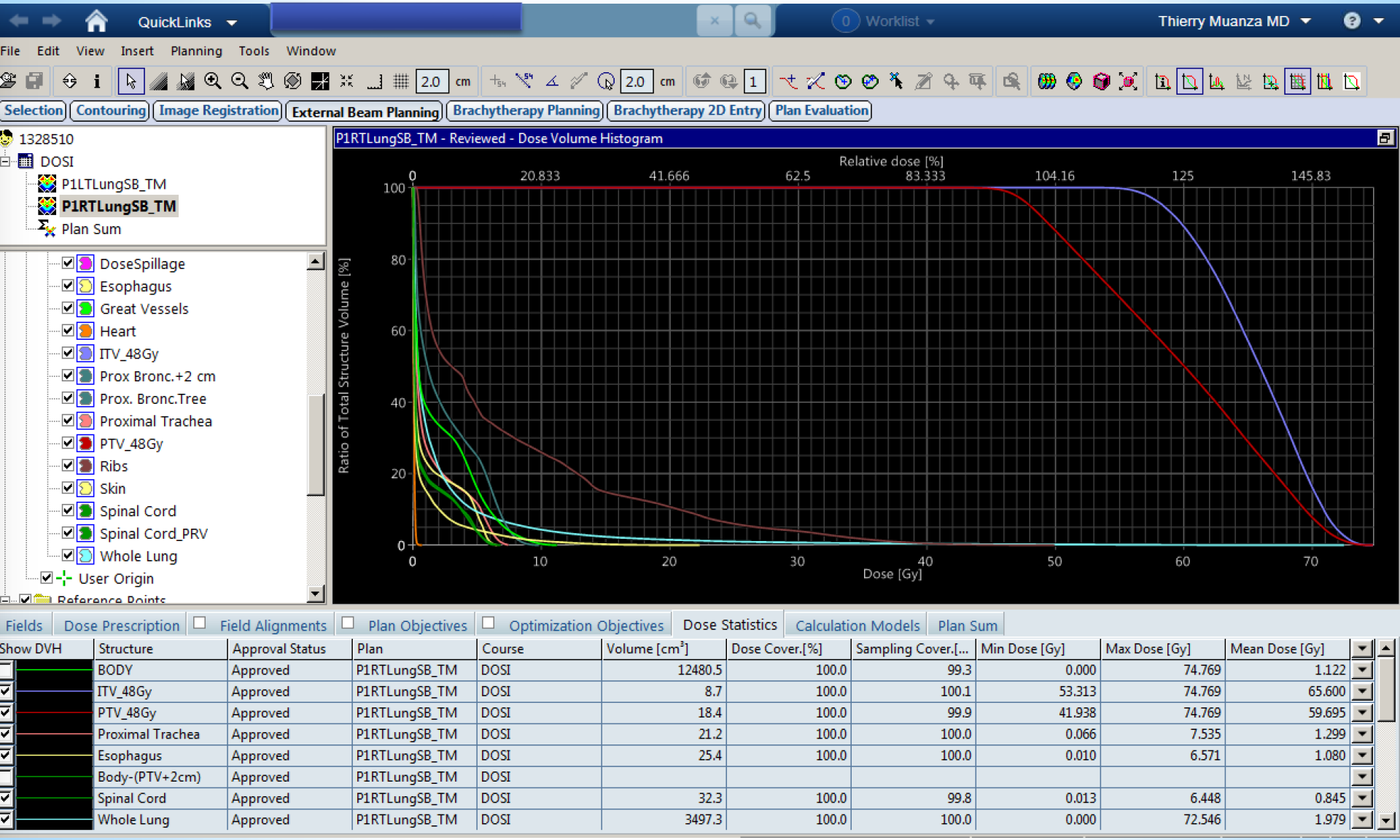
Y: -3.05 cm
Standard, HFS
Z: 6.00 cm
(cpapadopoulos 20/02/2015 9:29 AM)



Gro...	Field ID	Techniq...	Machine/Energy	MLC	Field Weig...	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wed...	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [c...	Calculat... SSD [cm]	MU	Ref. D [Gy]
☑	1.1 RA CW	ARC-I	Trilogy_a - 6X-SRS	VMAT	1.777	Varian I...	180.1 CW 45.0	30.0	0.0	None	5.1	+2.7	+2.4	4.7	+2.3	+2.4	-8.00	-3.20	6.80	86.9	2906	
☑	1.2 RA CCW	ARC-I	Trilogy_a - 6X-SRS	VMAT	1.778	Varian I...	45.0 CCW 180.1	330.0	0.0	None	5.1	+2.4	+2.7	4.7	+2.3	+2.4	-8.00	-3.20	6.80	92.7	2907	
☑	1. Post kV	STATIC-I	Trilogy_a - 6X-SRS		0.000	Varian I...	180.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-8.00	-3.20	6.80	86.9		
☑	1. Rt Lat kV	STATIC-I	Trilogy_a - 6X-SRS		0.000	Varian I...	270.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-8.00	-3.20	6.80	94.7		
☑	1.Ant CBCT	STATIC-I	Trilogy_a - 6X-SRS		0.000	Varian I...	0.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-8.00	-3.20	6.80	95.1		



Gro...	Field ID	Techniq...	Machine/Energy	MLC	Field Weig...	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wed...	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [c...	Calculat... SSD [cm]	MU	Ref. D [Gy]
☑	1.1 RA CW	ARC-I	Trilogy_a - 6X-SRS	VMAT	1.777	Varian I...	180.1 CW 45.0	30.0	0.0	None	5.1	+2.7	+2.4	4.7	+2.3	+2.4	-8.00	-3.20	6.80	86.9	2906	
☑	1.2 RA CCW	ARC-I	Trilogy_a - 6X-SRS	VMAT	1.778	Varian I...	45.0 CCW 180.1	330.0	0.0	None	5.1	+2.4	+2.7	4.7	+2.3	+2.4	-8.00	-3.20	6.80	92.7	2907	
☑	1. Post kV	STATIC-I	Trilogy_a - 6X-SRS		0.000	Varian I...	180.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-8.00	-3.20	6.80	86.9		
☑	1. Rt Lat kV	STATIC-I	Trilogy_a - 6X-SRS		0.000	Varian I...	270.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-8.00	-3.20	6.80	94.7		
☑	1.Ant CBCT	STATIC-I	Trilogy_a - 6X-SRS		0.000	Varian I...	0.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-8.00	-3.20	6.80	95.1		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Thierry Muanza MD
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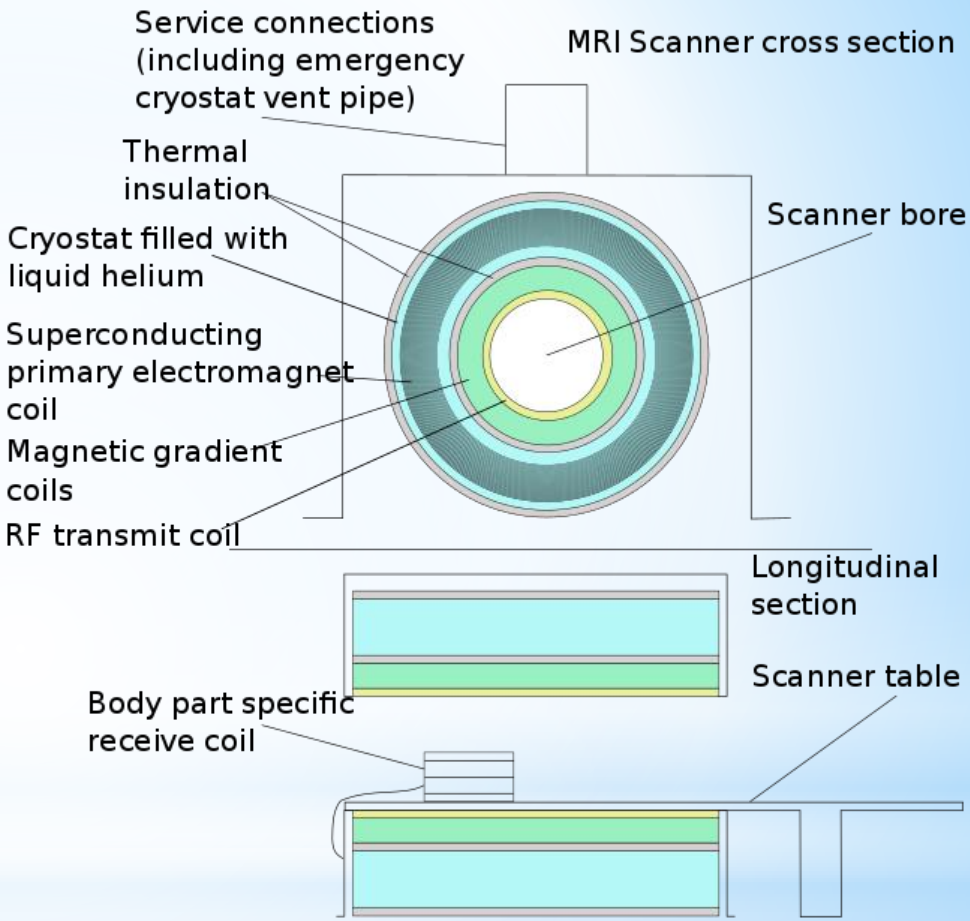
1328510
DOSI
P1LTLungSB_TM
P1RTLungSB_TM
Plan Sum
DoseSpillage
Esophagus
Great Vessels
Heart
ITV_48Gy
Prox Bronc.+2 cm
Prox. Bronc.Tree
Proximal Trachea
PTV_48Gy
Ribs
Skin
Spinal Cord
Spinal Cord_PRV
Whole Lung
User Origin
P1RTLungSB_TM - Reviewed - Dose Volume Histogram
Relative dose [%]
0 20.833 41.666 62.5 83.333 104.16 125 145.83
Ratio of Total Structure Volume [%]
100 80 60 40 20 0
0 10 20 30 40 50 60 70
Dose [Gy]
Fields Dose Prescription Field Alignments Plan Objectives Optimization Objectives Dose Statistics Calculation Models Plan Sum
Show DVH Structure Approval Status Plan Course Volume [cm³] Dose Cover.[%] Sampling Cover.[... Min Dose [Gy] Max Dose [Gy] Mean Dose [Gy]
BODY Approved P1RTLungSB_TM DOSI 12480.5 100.0 99.3 0.000 74.769 1.122
ITV_48Gy Approved P1RTLungSB_TM DOSI 8.7 100.0 100.1 53.313 74.769 65.600
PTV_48Gy Approved P1RTLungSB_TM DOSI 18.4 100.0 99.9 41.938 74.769 59.695
Proximal Trachea Approved P1RTLungSB_TM DOSI 21.2 100.0 100.0 0.066 7.535 1.299
Esophagus Approved P1RTLungSB_TM DOSI 25.4 100.0 100.0 0.010 6.571 1.080
Body-(PTV+2cm) Approved P1RTLungSB_TM DOSI
Spinal Cord Approved P1RTLungSB_TM DOSI 32.3 100.0 99.8 0.013 6.448 0.845
Whole Lung Approved P1RTLungSB_TM DOSI 3497.3 100.0 100.0 0.000 72.546 1.979

An MRI or magnetic resonance imaging is a radiology techinque scan that uses magnetism, radio waves, and a computer to produce images of body structures. The MRI scanner is a tube surrounded by a giant circular magnet. The patient is placed on a moveable bed that is inserted into the magnet. The magnet creates a strong magnetic field that aligns the protons of hydrogen atoms, which are then exposed to a beam of radio waves. This spins the various protons of the body, and they produce a faint signal that is detected by the receiver portion of the MRI scanner. A computer processes the receiver information, which produces an image.

MRI image and resolution is quite detailed, and it can detect tiny changes of structures within the body. For some procedures, contrast agents, such as gadolinium, are used to increase the accuracy of the images.

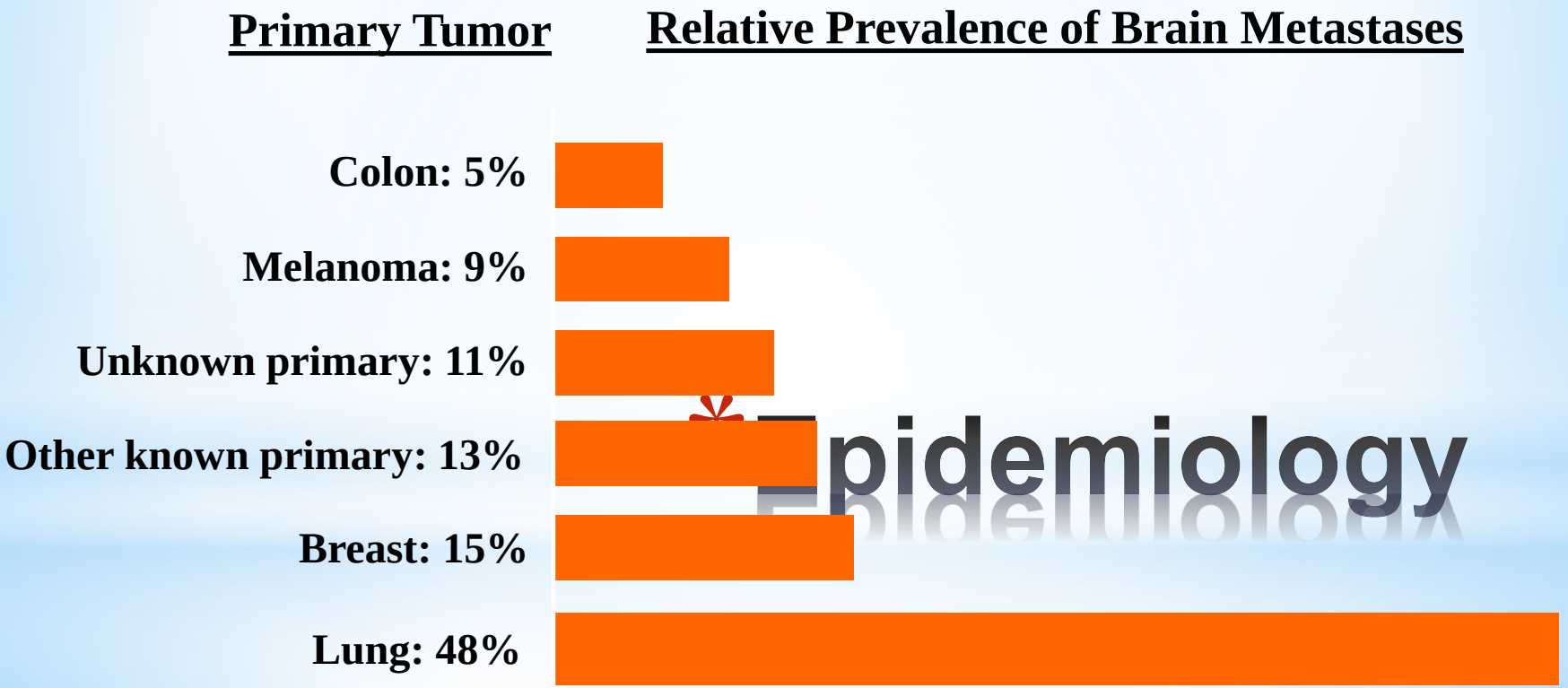


Brain Metastasis

* Most common intracranial tumours
  * 170,000 – 200,000 new diagnoses per year in US alone but precise incidence unknown.
  * Occur 25% - 30% of cancer patients
* Incidence increasing
  * Aging population, increase in cancer
  * Better treatment leading to prolonged survival and emergence of brain mets
* Mean age at presentation is 55-65 years

Kaye A, Laws E. London, NY: Churchil Livingstone; 2001

Most common source of brain mets: Lung cancer



Epidemiology

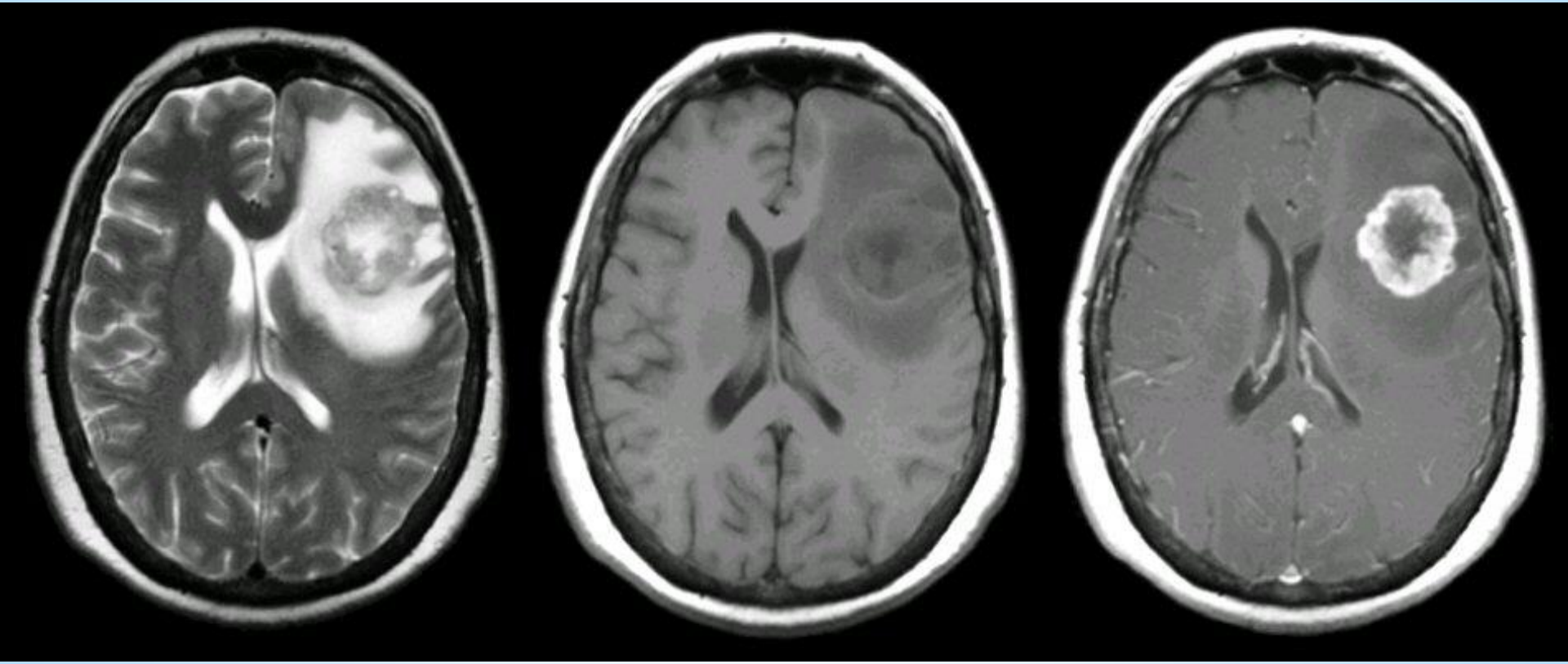
Wen PY, et al. In: DeVita VT Jr, et al (eds). *Cancer: Principles & Practice of Oncology.* 2001:2656-2670

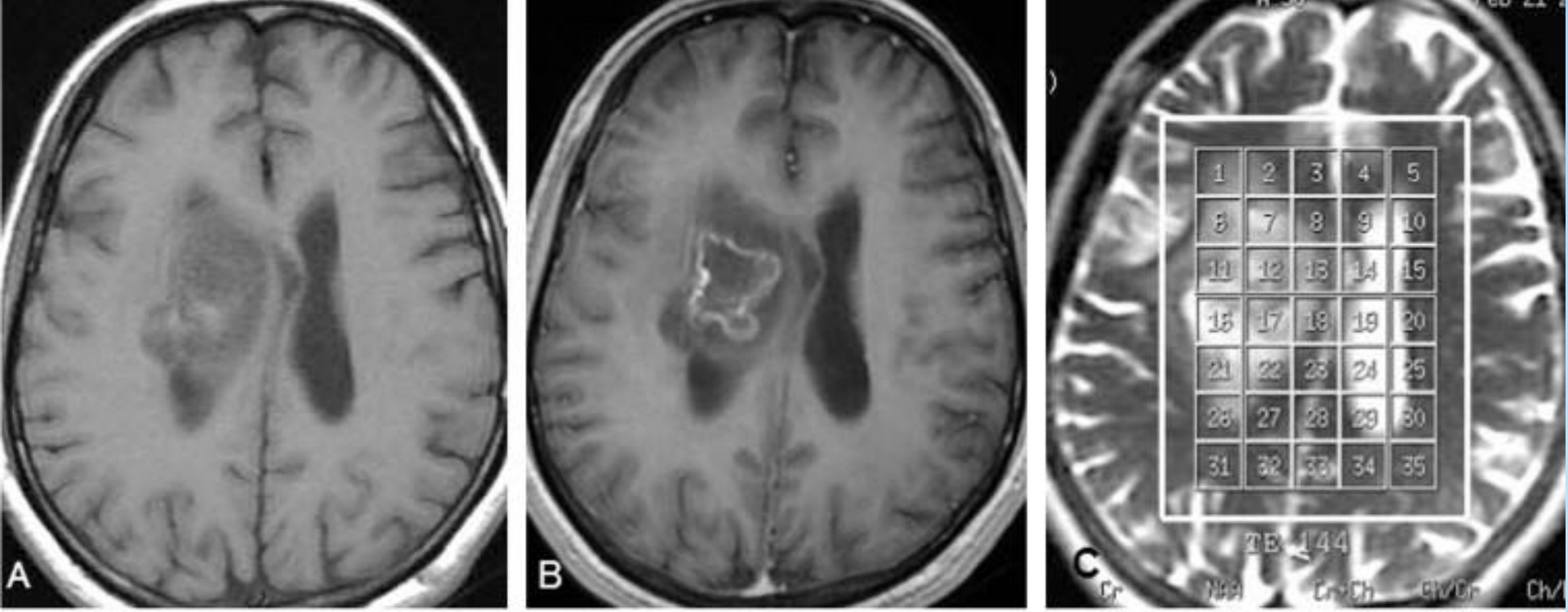
Pathophysiology

* Metastasis via **hematogenous** spread
* Tend to occur directly beneath the gray-white junction where blood vessels decrease in diameter, or the terminal “watershed areas” of arterial circulation
* Distribution according to relative blood flow
  * **Cerebral hemispheres (~80%)**
  * Cerebellum (15%)
  * Brain stem (5%)
  * Areas receiving more blood tend to have more mets

Treatment options

* Surgery +WBRT
* WBRT + SRS
* Surgery or SRS alone
* Surgery → SRS
* Best supportive care
* Chemotherapy




A
B
C
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6 7 8 9 10
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21 22 23 24 25
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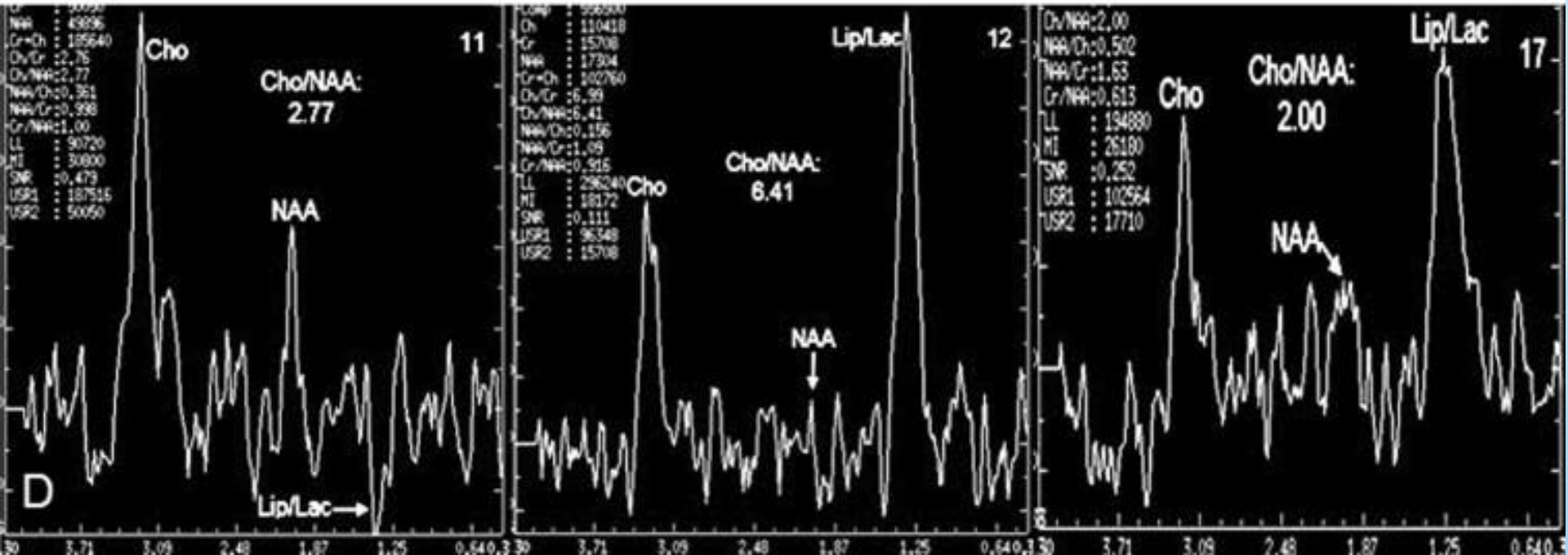
TE 144
Cr
NAA
Cr+Ch
Ch/Cr
Ch/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Cho/NAA:
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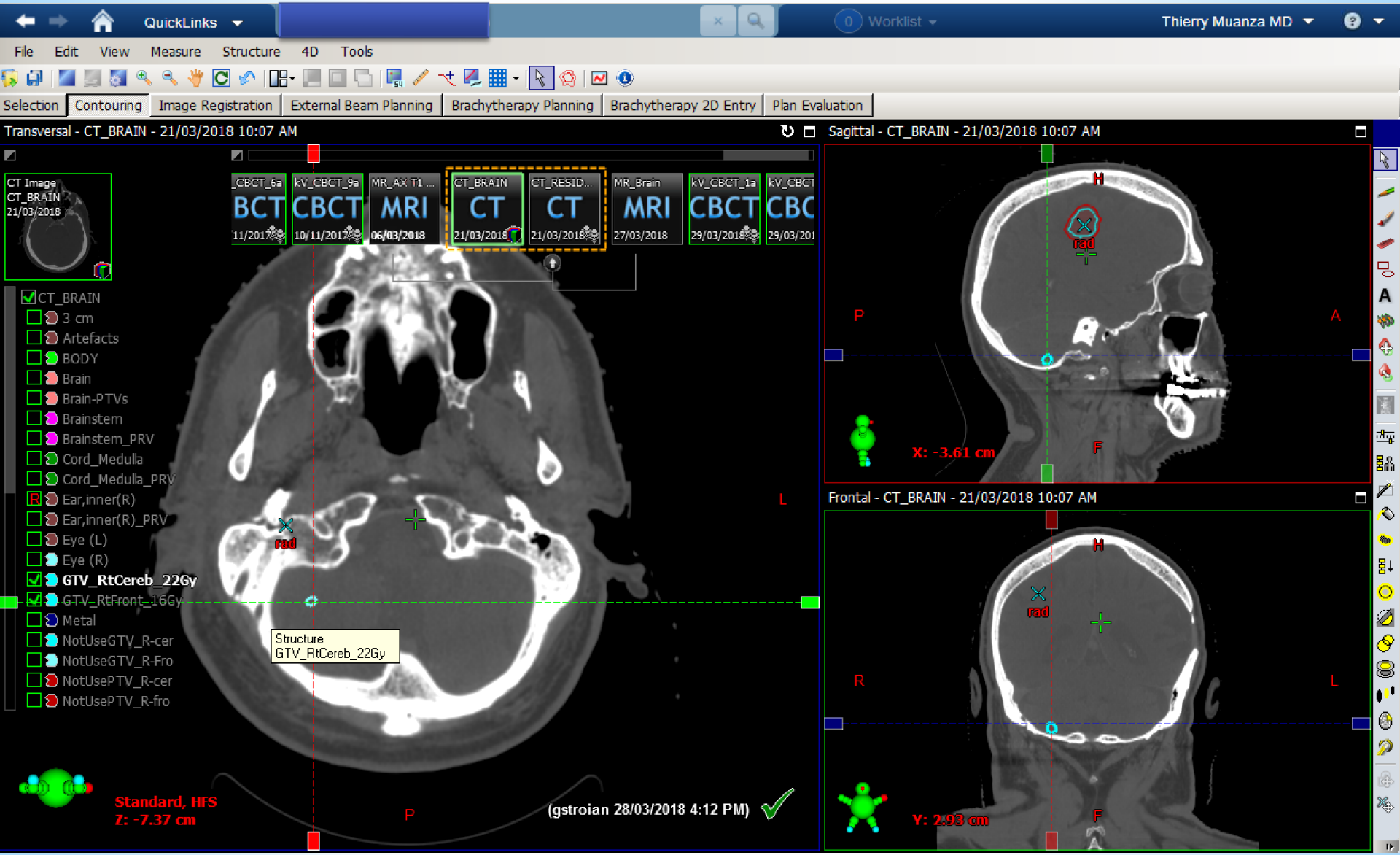
NAA
Lip/Lac
17
Cho/NAA:
2.00
Cho
NAA

Interpretation of Brain Metabolites Detected by ^{1}H-Magnetic Resonance Spectroscopy

- **Choline**—High levels indicate increased cellular activity and proliferation among glial cells. Because glial cells are involved in protective and restorative functions, increased glial activity implies a process reactive to a neoplasm.
- **Creatine**—Elevated levels are more consistent with tumor cells than with normal cells.
- **Lactate**—Increased levels indicate tumor metabolism. Neoplasms tend to consume glucose using only anaerobic pathways, thus producing increased lactate levels.
- **Myoinositol**—High levels indicate glial hypertrophy and proliferation, implying a process reactive to a neoplasm.
- **N-Acetylaspartate**—Reduced levels indicate neuronal damage or functional degeneration.

*SRS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External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
Transversal - CT_BRAIN - 21/03/2018 10:07 AM
Sagittal - CT_BRAIN - 21/03/2018 10:07 AM
Frontal - CT_BRAIN - 21/03/2018 10:07 AM
CT Image
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21/03/2018
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10/11/2017
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06/03/2018
CT_BRAIN
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MR_Brain
MRI
27/03/2018
kV_CBCT_1a
CBCT
29/03/2018
CT_BRAIN
3 cm
Artefacts
BODY
Brain
Brain-PTVs
Brainstem
Brainstem_PRV
Cord_Medulla
Cord_Medulla_PRV
Ear,inner(R)
Ear,inner(R)_PRV
Eye (L)
Eye (R)
GTV_RtCereb_22Gy
GTV_RtFront_16Gy
Metal
NotUseGTV_R-cer
NotUseGTV_R-Fro
NotUsePTV_R-cer
NotUsePTV_R-fro
rad
Structure
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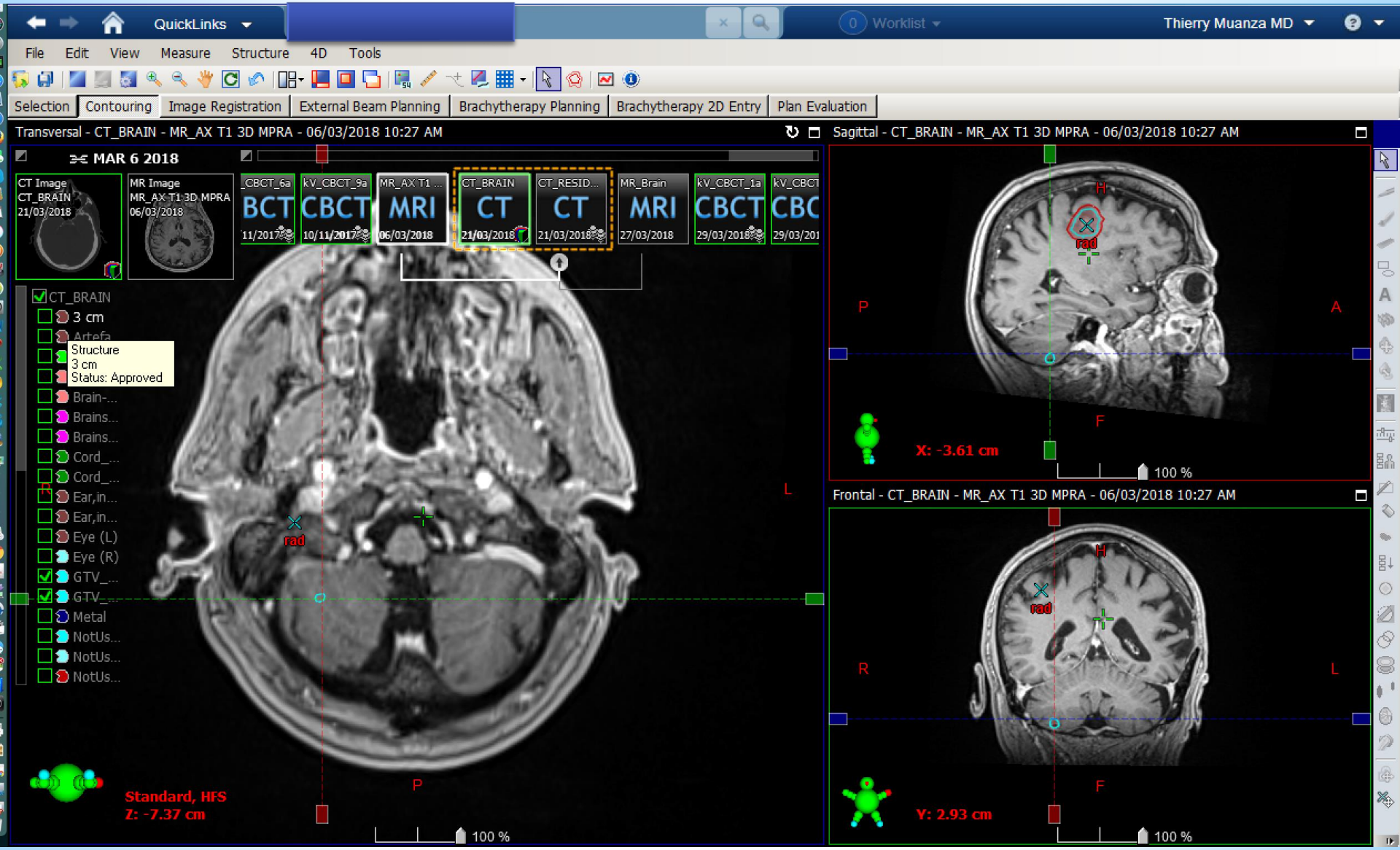
X: -3.61 cm
Y: 2.93 cm
Standard, HFS
Z: -7.37 cm
(gstroian 28/03/2018 4:12 PM)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Brachytherapy 2D Entry
Plan Evaluation
Transversal - CT_BRAIN - MR_AX T1 3D MPRA - 06/03/2018 10:27 AM
MAR 6 2018
CT Image
CT_BRAIN
21/03/2018
MR Image
MR_AX T1 3D MPRA
06/03/2018
CBCT
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CBCT
10/11/2017
MRI
06/03/2018
CT
21/03/2018
CT
21/03/2018
MRI
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CBCT
29/03/2018
CT_BRAIN
3 cm
Structure
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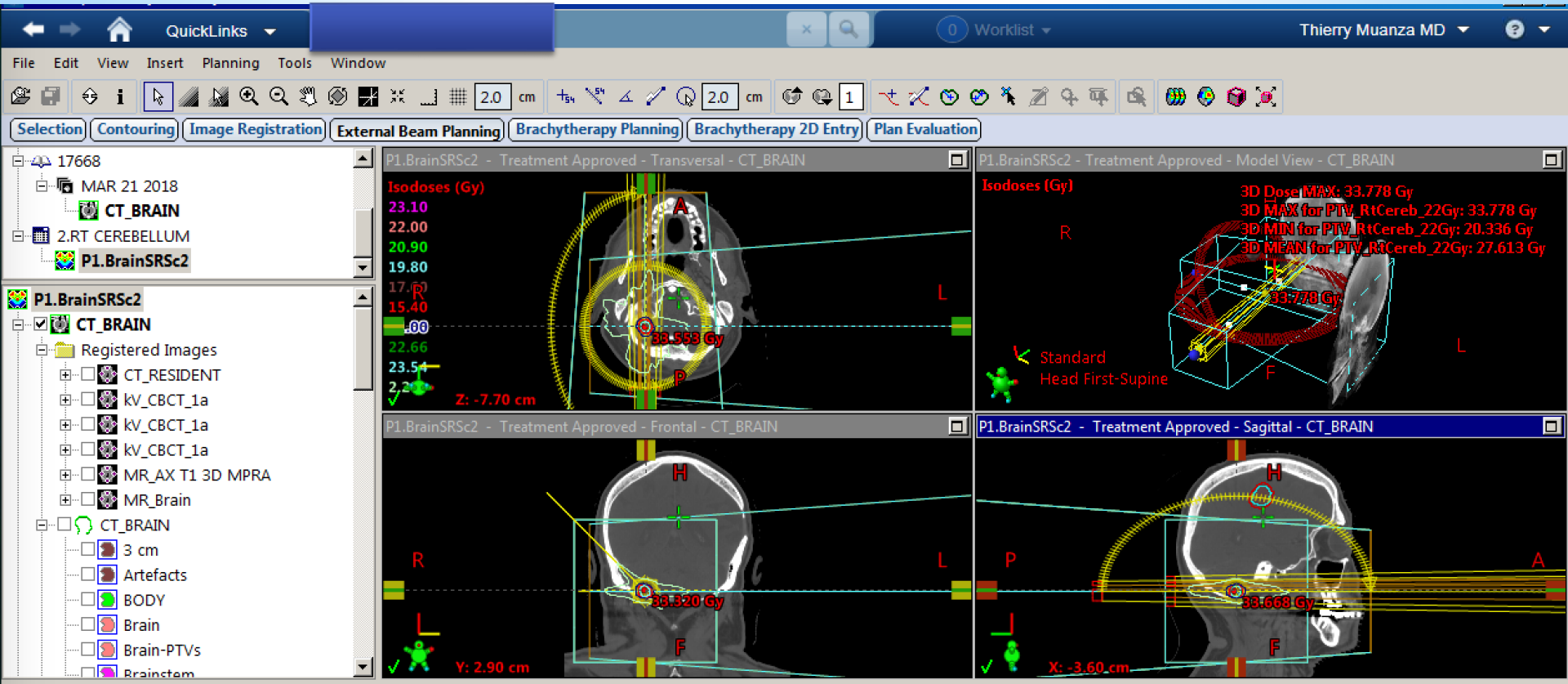
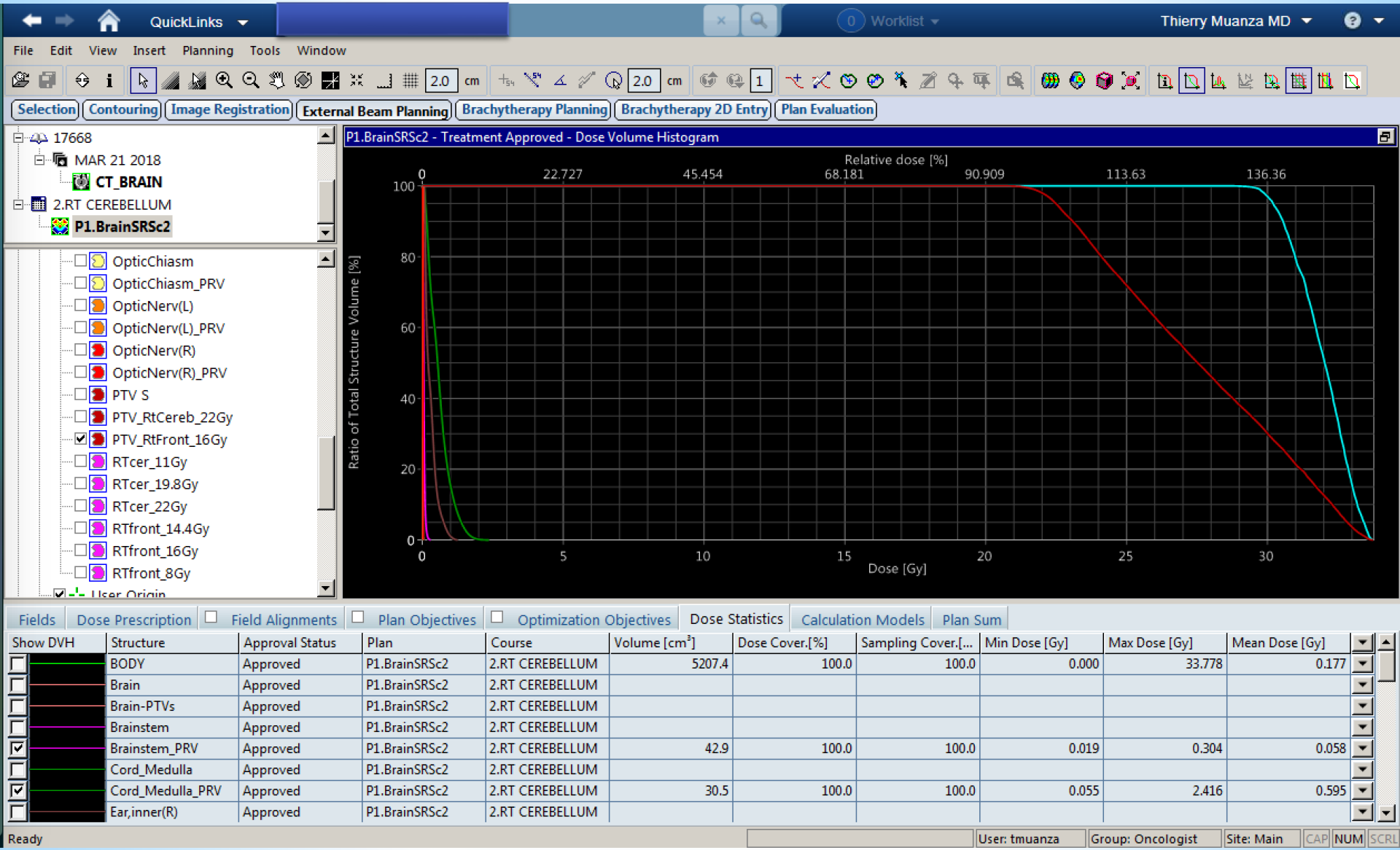
Brains...
Brains...
Cord_...
Cord_...
Ear,in...
Ear,in...
Eye (L)
Eye (R)
GTV_...
GTV_...
Metal
NotUs...
NotUs...
NotUs...
rad
L
P
Standard, HFS
Z: -7.37 cm
100 %
Sagittal - CT_BRAIN - MR_AX T1 3D MPRA - 06/03/2018 10:27 AM
H
rad
P
A
F
X: -3.61 cm
100 %
Frontal - CT_BRAIN - MR_AX T1 3D MPRA - 06/03/2018 10:27 AM
H
rad
R
L
F
Y: 2.93 cm
100 %



Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

Gro...	Field ID	Technique	Machine/Energy	MLC	Field Wei...	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wed...	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [c...	Z [cm]	Calculat... SSD [cm]	MU	Ref. D [Gy]
☑	1.1 RA CW	SRS ARC-I	TrueBeam_a - 6X-FFF	VMAT	2.773	Varian ...	180.1 CW 179.9	45.0	0.0	None	2.4	+1.2	+1.2	2.4	+1.2	+1.2	-3.60	2.90	-7.70	94.5	6183	
☑	1.2 RA CW T315	SRS ARC-I	TrueBeam_a - 6X-FFF	VMAT	1.317	Varian ...	180.1 CW 0.0	45.0	315.0	None	2.4	+1.2	+1.2	2.4	+1.2	+1.2	-3.60	2.90	-7.70	94.5	2936	
☑	1. Ant kV	STATIC-I	TrueBeam_a - 6X-FFF		0.000	Varian ...	0.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-3.60	2.90	-7.70	86.8		
☑	1. Rt Lat kV	STATIC-I	TrueBeam_a - 6X-FFF		0.000	Varian ...	270.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-3.60	2.90	-7.70	95.1		
☑	1.Ant CBCT	STATIC-I	TrueBeam_a - 6X-FFF		0.000	Varian ...	0.0	0.0	0.0	None	15.0	+7.5	+7.5	15.0	+7.5	+7.5	-3.60	2.90	-7.70	86.8		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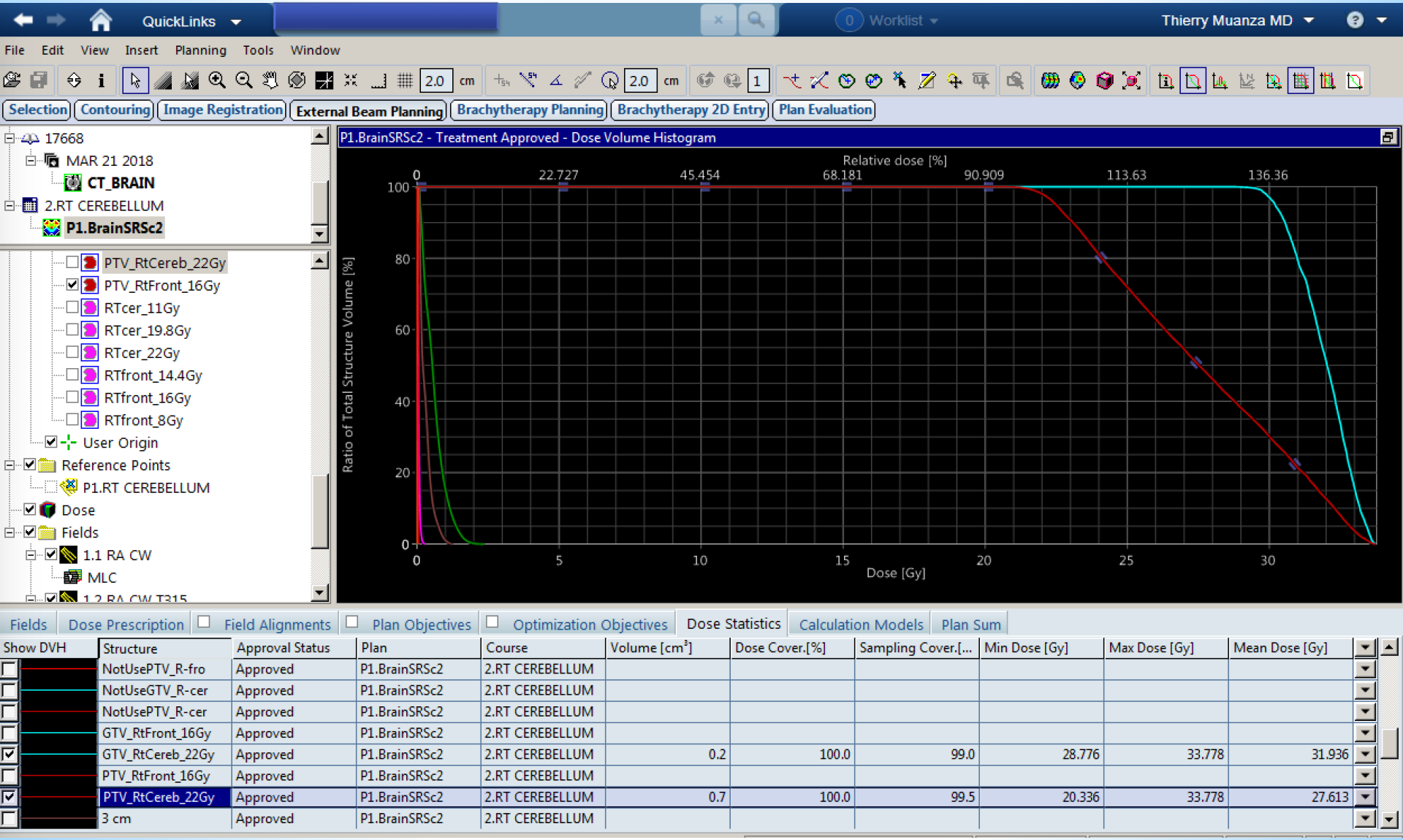
17668
MAR 21 2018
CT_BRAIN
2.RT CEREBELLUM
P1.BrainSRSc2
OpticChiasm
OpticChiasm_PRV
OpticNerv(L)
OpticNerv(L)_PRV
OpticNerv(R)
OpticNerv(R)_PRV
PTV S
PTV_RtCereb_22Gy
PTV_RtFront_16Gy
RTcer_11Gy
RTcer_19.8Gy
RTcer_22Gy
RTfront_14.4Gy
RTfront_16Gy
RTfront_8Gy
P1.BrainSRSc2 - Treatment Approved - Dose Volume Histogram
Relative dose [%]
0 22.727 45.454 68.181 90.909 113.63 136.36
Ratio of Total Structure Volume [%]
100 80 60 40 20 0
0 5 10 15 20 25 30
Dose [Gy]
Fields Dose Prescription Field Alignments Plan Objectives Optimization Objectives Dose Statistics Calculation Models Plan Sum
Show DVH | Structure | Approval Status | Plan | Course | Volume [cm³] | Dose Cover.[%] | Sampling Cover.[... | Min Dose [Gy] | Max Dose [Gy] | Mean Dose [Gy]
BODY | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM | 5207.4 | 100.0 | 100.0 | 0.000 | 33.778 | 0.177
Brain | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM
Brain-PTVs | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM
Brainstem | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM
Brainstem_PRV | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM | 42.9 | 100.0 | 100.0 | 0.019 | 0.304 | 0.058
Cord_Medulla | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM
Cord_Medulla_PRV | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM | 30.5 | 100.0 | 100.0 | 0.055 | 2.416 | 0.595
Ear,inner(R) | Approved | P1.BrainSRSc2 | 2.RT CEREBELLUM
Ready
User: tmuanza
Group: Oncologist
Site: Main
CAP NUM SCRL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17668
MAR 21 2018
CT_BRAIN
2.RT CEREBELLUM
P1.BrainSRSc2
PTV_RtCereb_22Gy
PTV_RtFront_16Gy
RTcer_11Gy
RTcer_19.8Gy
RTcer_22Gy
RTfront_14.4Gy
RTfront_16Gy
RTfront_8Gy
User Origin
Reference Points
P1.RT CEREBELLUM
Dose
Fields
1.1 RA CW
MLC
P1.BrainSRSc2 - Treatment Approved - Dose Volume Histogram
Relative dose [%]
0 22.727 45.454 68.181 90.909 113.63 136.36
Ratio of Total Structure Volume [%]
100 80 60 40 20 0
0 5 10 15 20 25 30
Dose [Gy]
Fields Dose Prescription Field Alignments Plan Objectives Optimization Objectives Dose Statistics Calculation Models Plan Sum
Show DVH Structure Approval Status Plan Course Volume [cm³] Dose Cover.[%] Sampling Cover.[... Min Dose [Gy] Max Dose [Gy] Mean Dose [Gy]
NotUsePTV_R-fro Approved P1.BrainSRSc2 2.RT CEREBELLUM
NotUseGTV_R-cer Approved P1.BrainSRSc2 2.RT CEREBELLUM
NotUsePTV_R-cer Approved P1.BrainSRSc2 2.RT CEREBELLUM
GTV_RtFront_16Gy Approved P1.BrainSRSc2 2.RT CEREBELLUM
GTV_RtCereb_22Gy Approved P1.BrainSRSc2 2.RT CEREBELLUM 0.2 100.0 99.0 28.776 33.778 31.936
PTV_RtFront_16Gy Approved P1.BrainSRSc2 2.RT CEREBELLUM
PTV_RtCereb_22Gy Approved P1.BrainSRSc2 2.RT CEREBELLUM 0.7 100.0 99.5 20.336 33.778 27.613
3 cm Approved P1.BrainSRSc2 2.RT CEREBELLUM

Critical Structures

Priority	Organ	Parameter	Deviation		
			Major	Minor	Compliant
1	Brainstem PRV	Dmax (Gy)	> 10 Gy	10 Gy to 8 Gy	< 8 Gy
1	Cord PRV	Dmax (Gy)	> 10 Gy	10 Gy to 8 Gy	< 8 Gy
1	Optic Chiasm PRV	Dmax (Gy)	> 10 Gy	10 Gy to 8 Gy	< 8 Gy
1	Optic Nerve PRV (R)	Dmax (Gy)	> 10 Gy	10 Gy to 8 Gy	< 8 Gy
1	Optic Nerve PRV (L)	Dmax (Gy)	> 10 Gy	10 Gy to 8 Gy	< 8 Gy
2	Brain-PTV	V[10 Gy] (cc)	> 12 cc	12 cc to 10 cc	< 10 cc

Figure 3–1: The evaluation template for critical structures in planning SRS. The template was created with literature review [32, 33] and collaboration with physicians from our clinic. Each item in plan evaluation was given a priority number for its importance for adherence during treatment planning.

Target Evaluation

Target Name: PTV_Brain_18gy

Prescription Dose: 18.0 Gy

			Deviation		
Priority	**Criterion**	**Parameter**	**Major**	**Minor**	**Compliant**
2	Coverage	V[100% of P.D.] (%)	< 95%	95% to 98%	≥ 98%
		D[99%] (% of P.D.)	< 95%	95% to 98%	≥ 98%
3	Dose Conformality	PIV/TV	> 2	2 to 1.2	< 1.2
4	Dose homogeneity	MD/PD	< 1, or > 2	1 to 1.4, or 1.6 to 2	1.4 to 1.6
5	Dose fall-off	90%/50% Fall off (mm)	> 6 mm	6 mm to 4 mm	< 4 mm

Figure 3–2: The target evaluation template in planning SRS. The template was based on literature review [16, 17] and in collaboration with physicians from our clinic. The template evaluates TCP on the basis of coverage, dose conformity, dose homogeneity, and dose fall-off.

Web Application in Radiotherapy: the Standardization of Treatment Planning and Development of Quantitative Plan Quality Metrics

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Master of Science

Medical Physics Unit

McGill University

Montreal,Quebec

2013-07-15

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of
Master of Science

International Journal of Radiation Oncology biology • physics
Official Journal of the American Society for Radiation Oncology ASTRO

Online RTP Evaluator for SRS: A Single-Institute Experience

S.I. Shakir, K. Sultanem, G. Stroian, F. DeBlois, M. Fan, T.M. Muanza

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BRACHYTHERAPY

* Brachytherapy is a form of radiotherapy where a sealed radiation source is placed inside or next to the area requiring treatment.
  * Intracavitary/intraluminal/interstitial
  * LDR: 0.4 and 2 Gy/hr
  * HDR: ≥12 Gy/hr
* Inverse Square Law:
  * The tissues around the treated tumour receive a much lower dose than anticipated by other radiation methods.

Inverse Square Law

- The *intensity* of radiation at a given distance from a point source is *inversely proportional* to the *square* of the *distance* of the object from the source
- When the distance from the x-ray target is doubled, the intensity is ¼ as much as the original exposure
- Formula

$$\frac{I_1}{I_2} = \frac{d_2^2}{d_1^2}$$

Commonly used radiation sources (radionuclides) for brachytherapy.[74]

Radionuclide	Type	Half-life	Energy
Cesium-131 (^{131}Cs)	Electron Capture, ε	9.7 days	30.4 keV (mean)
Cesium-137 (^{137}Cs)	β^-- particles, γ-rays	30.17 years	0.512, 0.662 MeV γ-rays
Cobalt-60 (^{60}Co)	β^-- particles, γ-rays	5.26 years	1.17, 1.33 MeV γ-rays
Iridium-192 (^{192}Ir)	γ-rays	73.8 days	0.38 MeV (mean)
Iodine-125 (^{125}I)	Electron Capture, ε	59.6 days	27.4, 31.4 and 35.5 keV
Palladium-103 (^{103}Pd)	Electron Capture, ε	17.0 days	21 keV (mean)
Ruthenium-106 (^{106}Ru)	β^-- particles	1.02 years	3.54 MeV
Radium-226 (^{226}Ra)	β^-- particles	1599 years	

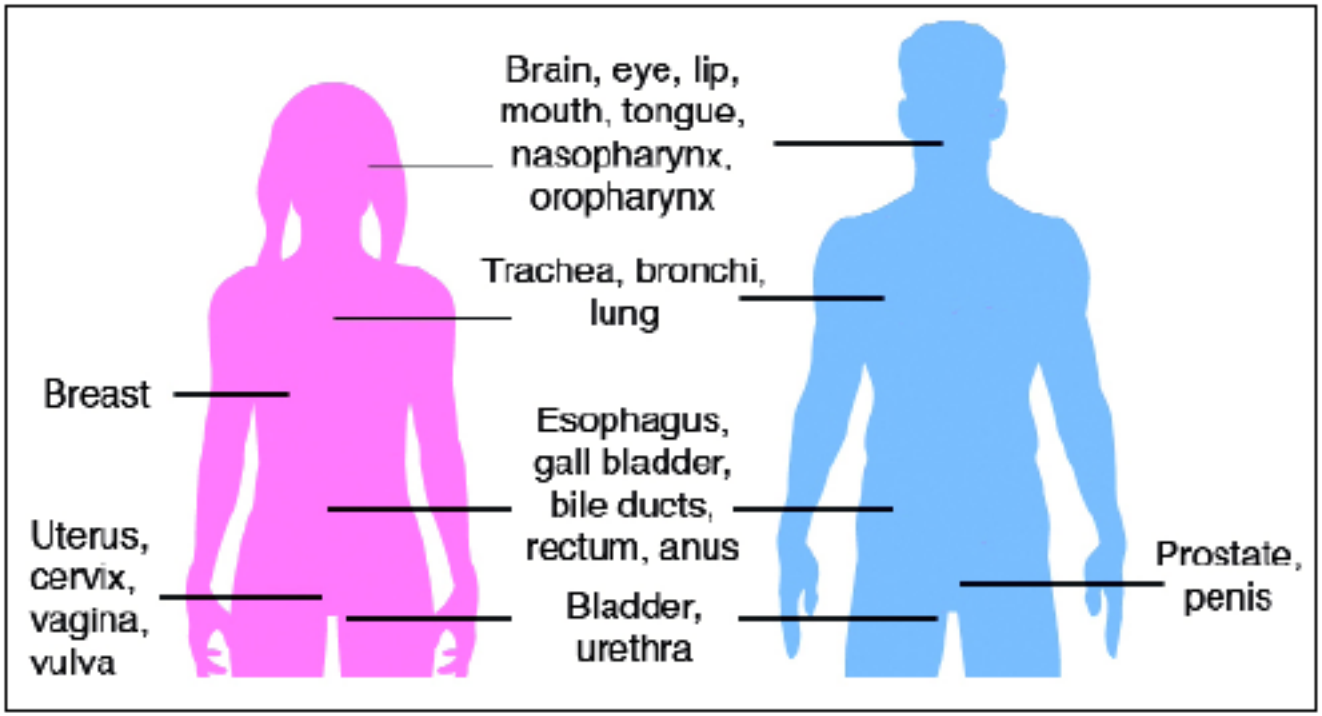
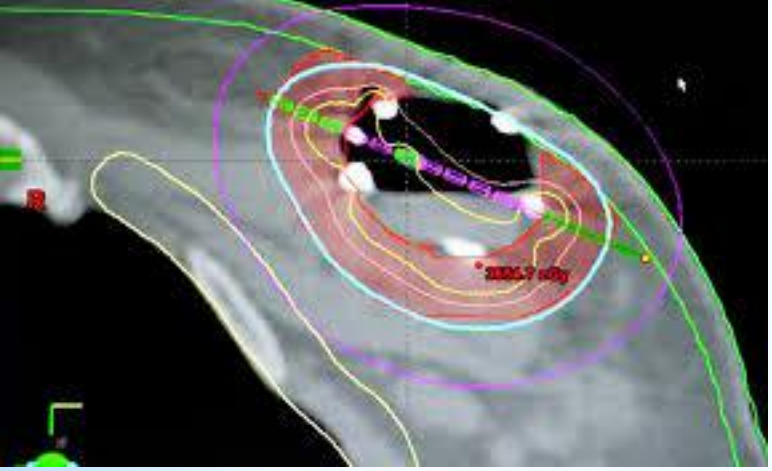
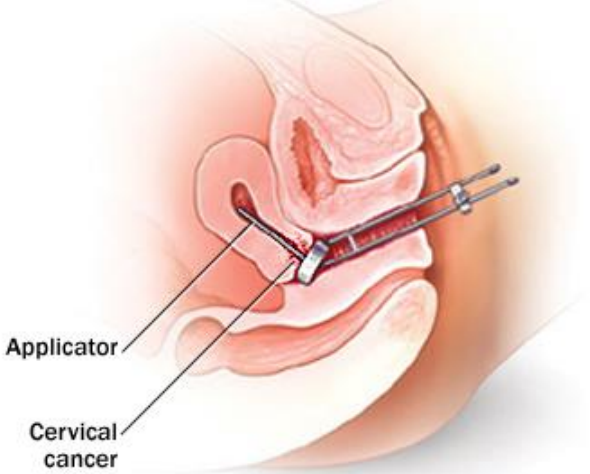
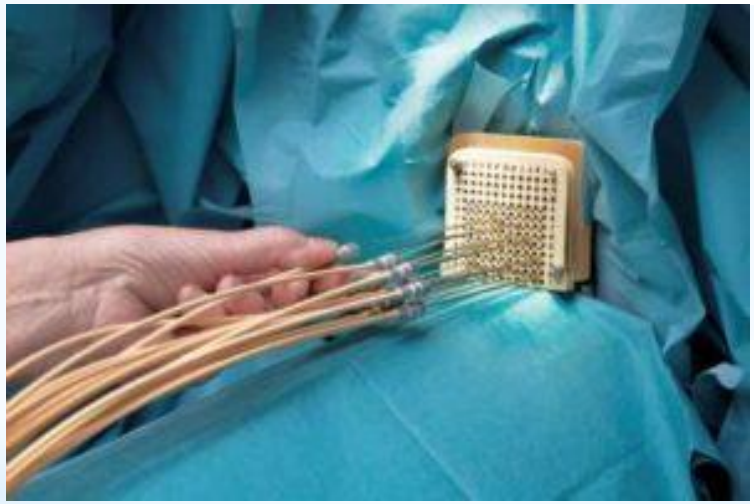


FIGURE 1

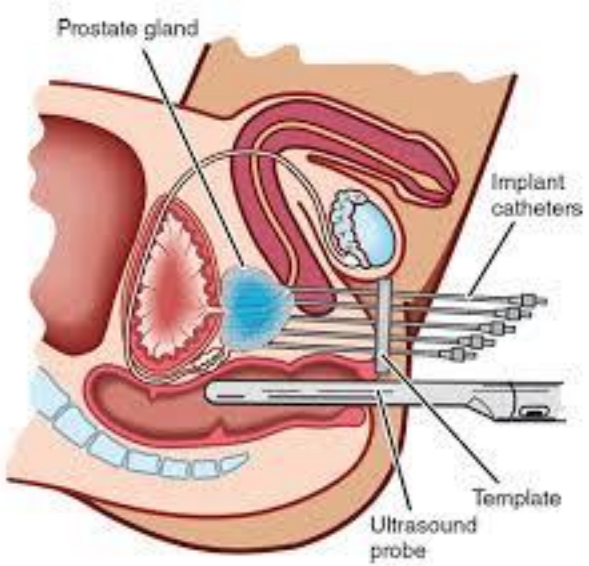
Body sites in which brachytherapy can be used to treat cancer.



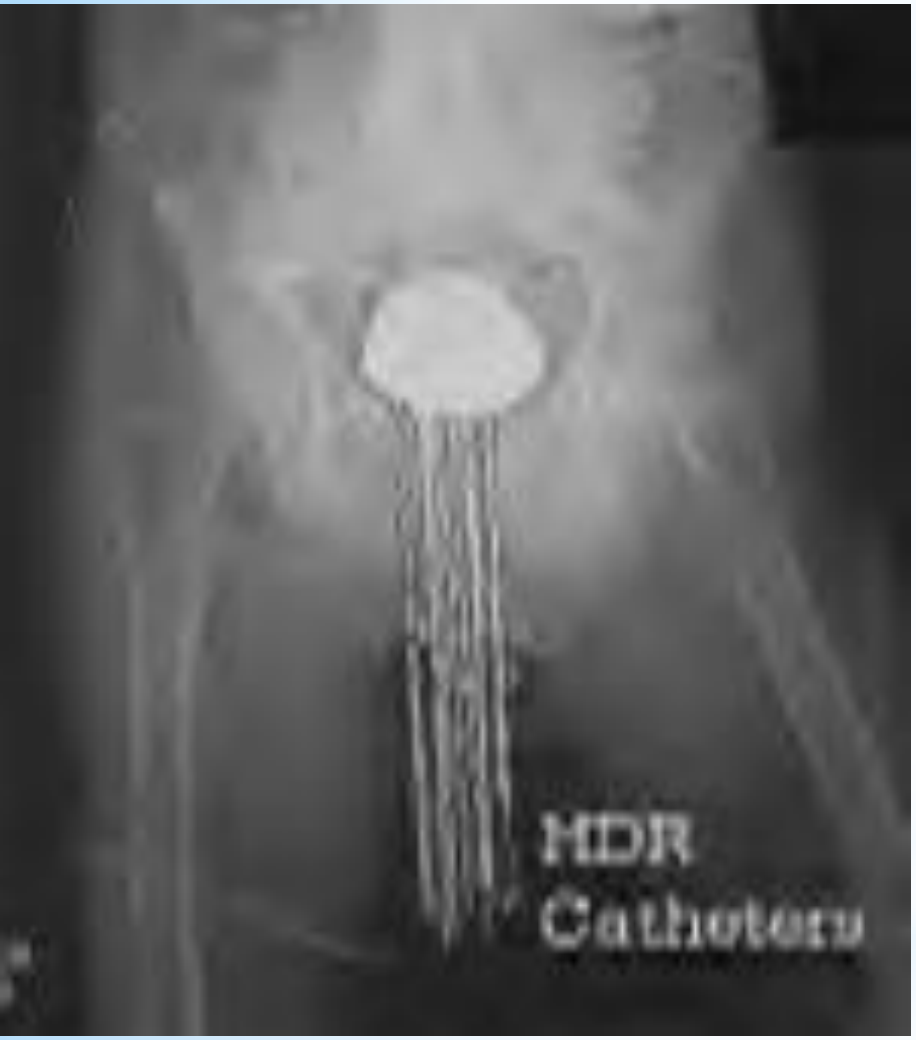


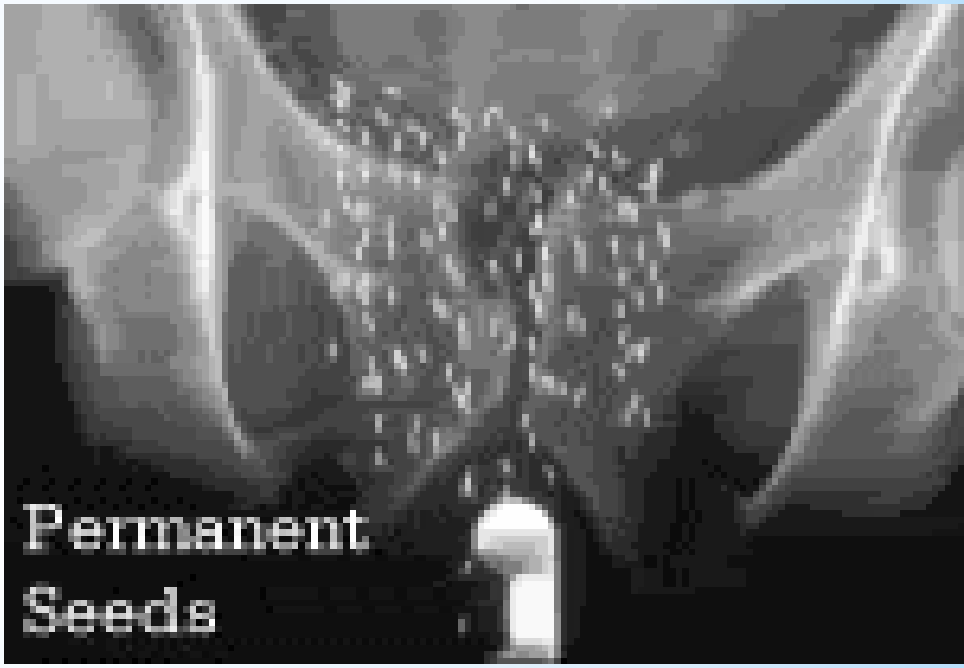


Brachytherapy is a safe and effective treatment for many types of cancer



BRACHYHDR remote afterloader


HDR
Catheter


Permanent
Seeds

* Role of Radiotherapy:

* Cancer treatment:
  * Curative Primary:
    * Prostate cancer.
    * Cancer of the head and neck region (early stage)
    * Hodgkin's disease.
    * Cervix cancer.
  * Curative as part of a combined approach:
    * Lung cancer.
    * Non-Hodgkin Lymphoma.
    * Cancer of the Head and Neck Region (advanced stage)
    * GI malignancies

* Role of Radiotherapy:

* Cancer treatment:
  * Curative Adjuvant to surgery:
    * Breast cancer.
    * Sarcoma.
    * Cancer of the Head and Neck region.
    * Carcinoma of the rectum.
    * Tumors of the Central Nervous Systems

* Role of Radiotherapy:

* Cancer treatment:
  * Palliative treatment:
    * Pain: Bone metastasis
    * Bleeding: Hemoptysis, Hematuria.
    * Obstructive or compressive symptoms:
      * Superior vena cava
      * Spinal cord compression
    * Brain metastasis.

* Role of Radiotherapy:

* Treatment of begnin disease:
  * Prophylaxis of heterotopic bone formation.
  * Arterio-venous malformation.
  * Grave's disease.
  * Keloids.
  * Pterygium.

Timing and clinical manifestation of radiation injury

1. Acute clinical period	0-6 months
2. Sub-acute period	6-12 months
3. Chronic clinical period	1-5 years
4. Late clinical period	

Acute versus late injury

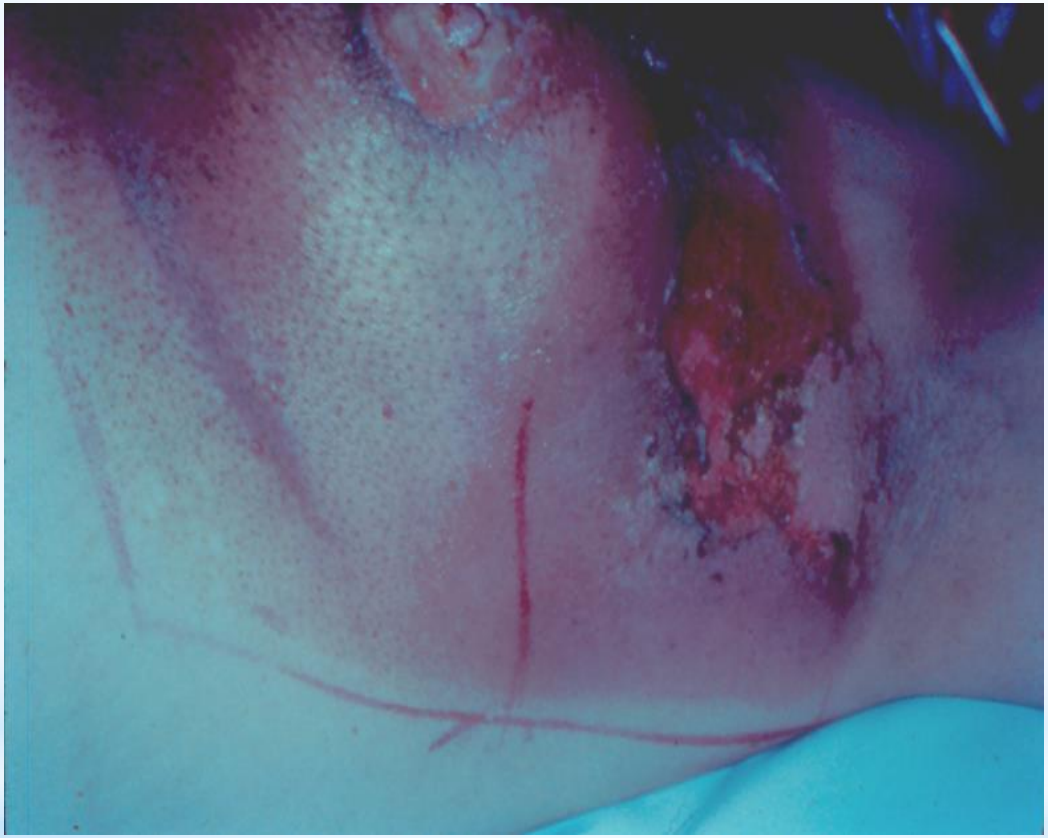
* Timing depends on cell cycle kinetics
* Clinical importance: reversible versus irreversible
* Correlation between acute and late complications

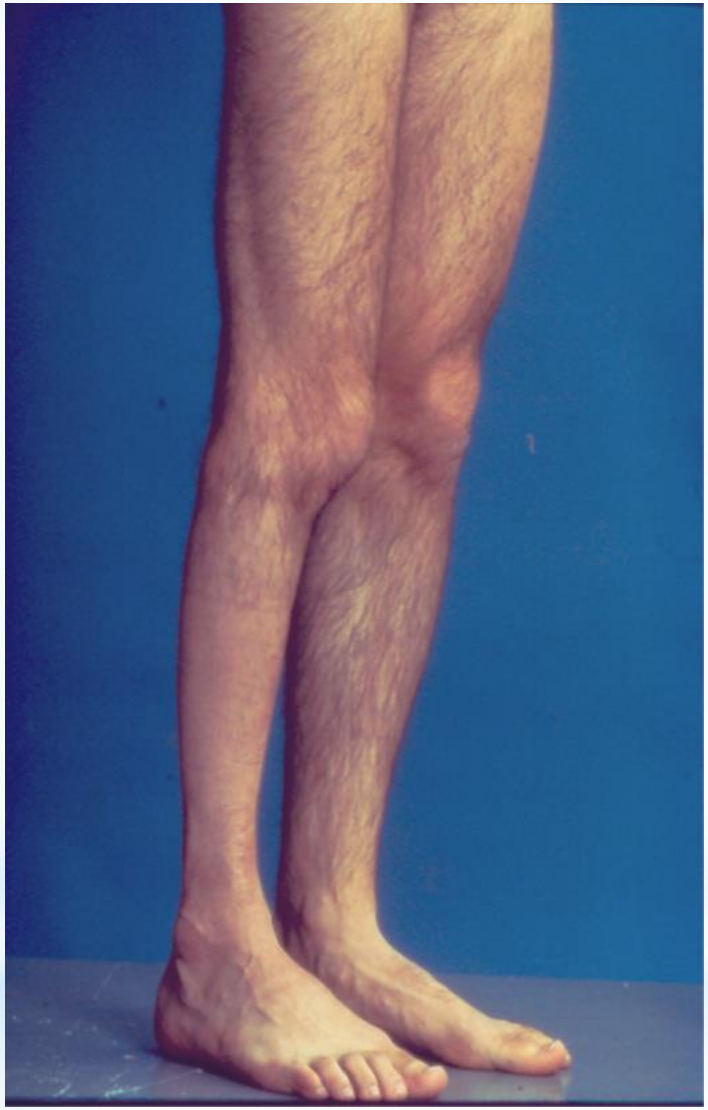
Factors affecting radiation damage

* 1. Volume to be irradiated
* 2. Total dose
* 3. Fraction size
* 4. Concomitant treatment

*Total body irradiation

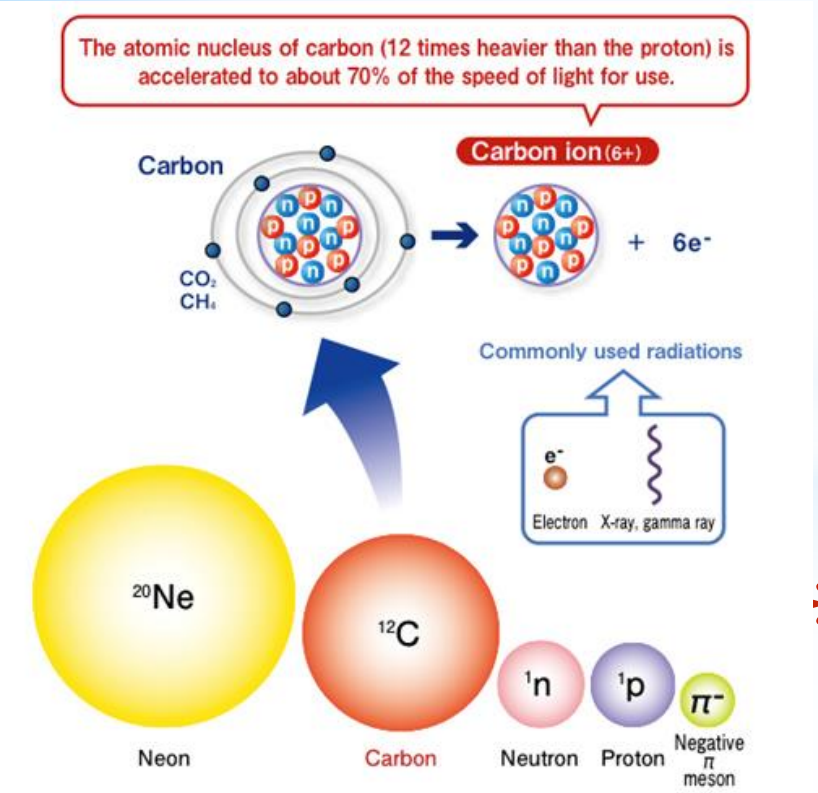
	Dose	Effects
Group I	0.5-1.5 Gy	Minimal
Group II	1.5- 4 Gy	Mild N/V
Group III	4- 6 Gy	Hemopoietic
Group IV	6- 14 Gy	GI
Group V	> 50 Gy	CNS

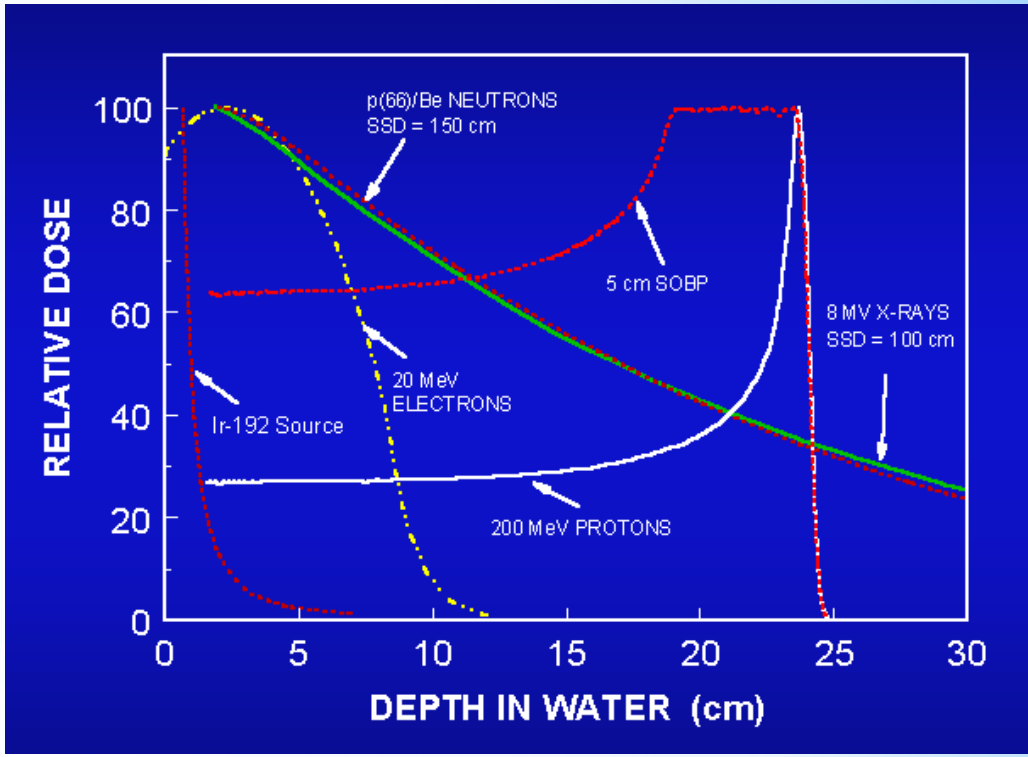




Radiation-Induced Malignancy

- 1. There is no threshold
- 2. Long latent period
- 3. Within the radiation ports
- 4. Different organ sensitivity
  - Thyroid, breast, lungs
  - Skeletal muscle





* Charged Particles Therapy

MAGICAL PROTONS?

MICHAEL GOITEIN, PH.D.

Harvard Medical School, Boston, MA; and Windisch, Switzerland

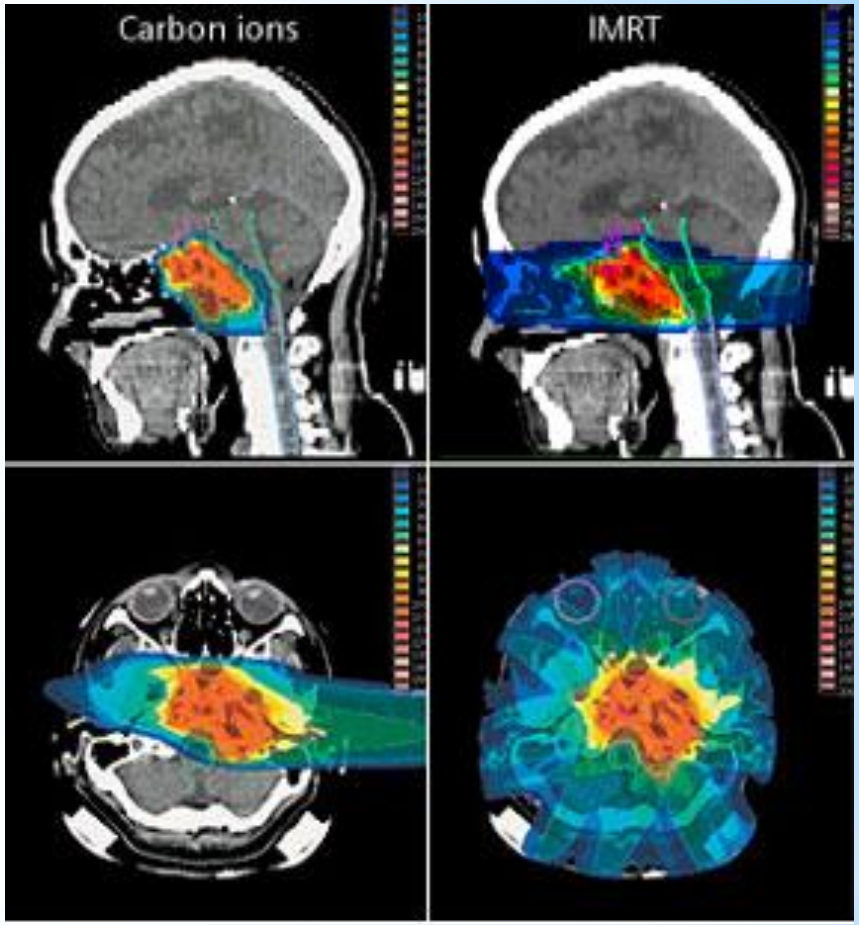
Proton therapy has enjoyed a recent surge of interest. Dozens of new proton centers are being planned, in addition to the approximately 24 now in operation worldwide (1). This enthusiasm is based, in part, on a conviction that the physical advantages of protons have been, in at least some sites, reflected in clinical advantages. The interest in protons has also been fueled by the perception that, although (or, perhaps, because) proton facilities are expensive, proton therapy can be highly profitable.

I find it hard not to be pleased about this growth. However, it carries dangers. Protons are not magical; the mere exposure to protons does not, in itself, doom proliferating malignant cells to their graves. Protons must be used well and, in this connection, I want to sound a few notes of caution.

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 654–656, 2008

0360-3016/08/$-see front matter

* Advantages
  * Superior dose distribution vs. photons
* Hypothesis
  * Improvement in treatment-related toxicity
  * Would allow for dose-escalation studies
  * Should improve local control
  * May improve overall survival



VOLUME 26 · NUMBER 15 · MAY 20 2008

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Should Randomized Clinical Trials Be Required for Proton Radiotherapy? An Alternative View

Eli Glatstein, *Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, PA*
John Glick, *Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA*
Larry Kaiser, *Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA*
Stephen M. Hahn, *Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA*

The facts offered by Goitein and Cox are incontrovertible in that the dose distribution of proton therapy is superior that of to x-rays. The question really has to do with whether or not these facts translate into *measurable benefits* for patients, and how significant those gains may be. The editorial in question alluded to a prior article in *JCO* by

Goitein and Cox believe that the superiority of protons rests largely on an improvement of the dose distribution that will almost certainly make for less morbidity. Exploiting that improvement in treatment-related toxicity suggests that dose escalation is feasible and that an improvement of local control should follow. Though local

Nonetheless, there is a potential for clinical benefit to be derived from proton therapy compared with conventional x-rays, either from dose escalation and improved local control and/or survival, or from reduced treatment-related morbidity, especially in children. Another important consideration is the potential for increased secondary cancers from proton therapy that has been postulated on a theoretical basis by Hall[3] in a recent article. Of course, Hall makes such predic-

community, whether we admit it or not. The enormous expenditures to build a proton center at the moment mean that during the next 5 to 10 years, there will be a relatively small number of facilities that have proton beam therapy.[12] The rest of the radiotherapeutic community will be interested in the outcomes to see if they really need to obtain such technology. It is likely that well-designed clinical trials that randomly assign proton beam therapy to patients would be supported by the National Cancer Institute and possibly even third-party payers themselves. To accrue the required numbers for such studies would probably require a concerted effort from virtually all the major centers

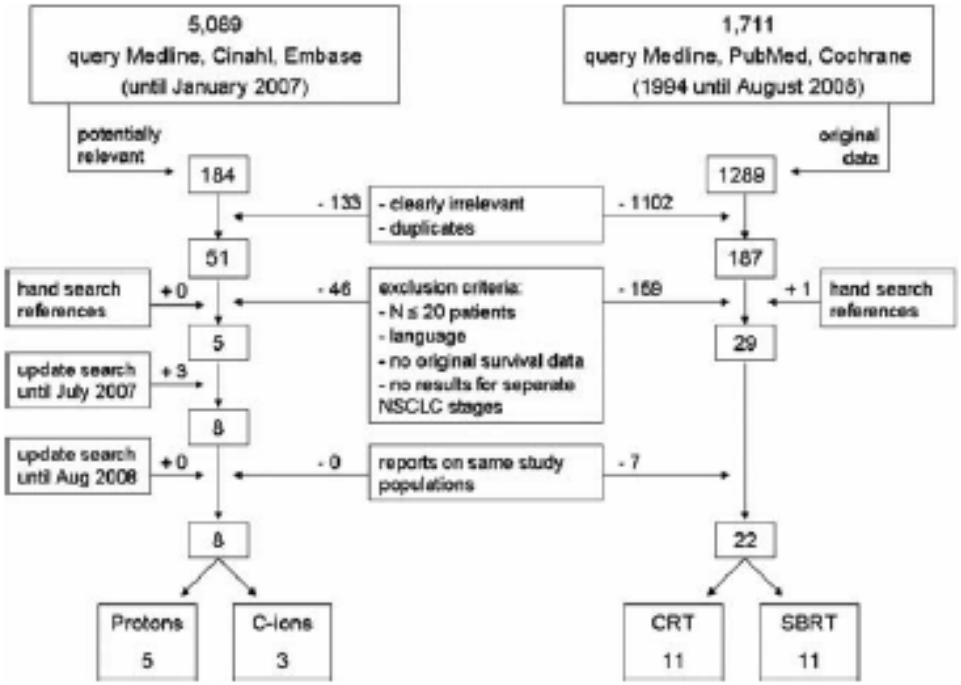
Meta-analysis

Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: A meta-analysis

Janneke P.C. Grutters [a,*], Alfons G.H. Kessels [b], Madelon Pijls-Johannesma [a], Dirk De Ruysscher [a], Manuela A. Joore [b,1], Philippe Lambin [a,1]

[a] Department of Radiation Oncology (MAASTRO Clinic), Maastricht University Medical Centre, The Netherlands
[b] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, The Netherlands

Appendix 1. Flow diagram of the search results for particle therapy (left) and photon therapy (right)



Results of meta-analysis for 2-year (disease-specific) survival.*

Treatment	2-year overall survival	(95% CI)	p-Value**		
			SBRT	Protons	Carbon-ions
CRT	0.531	(0.464–0.599)	<0.001	0.310	0.006
SBRT	0.702	(0.633–0.770)		0.262	0.638
Protons	0.612	(0.474–0.750)			0.180
Carbon-ions	0.737	(0.609–0.864)			
	2-year disease-specific survival				
CRT	0.674	(0.587–0.761)	0.006	0.430	0.065
SBRT	0.834	(0.751–0.917)		0.246	0.797
Protons	0.740	(0.607–0.874)			0.391
Carbon-ions	0.815	(0.700–0.930)			

Results of meta-analysis for 5-year (disease-specific) survival.*

Treatment	5-year overall survival	(95% CI)	p-Value**		
			SBRT	Protons	Carbon-ions
CRT	0.195	(0.148–0.242)	<0.001	0.014	<0.001
SBRT	0.421	(0.341–0.501)		0.782	0.985
Protons	0.397	(0.245–0.550)			0.790
Carbon-ions	0.421	(0.322–0.520)			
	5-year disease-specific survival				
CRT	0.435	(0.311–0.559)	0.045	0.471	0.051
SBRT	0.627	(0.500–0.754)		0.389	0.999
Protons	0.521	(0.319–0.724)			0.353
Carbon-ions	0.643	(0.486–0.801)			

Occurrence of adverse events grade 3–5* for each treatment modality in patients with stage I NSCLC.

Treatment	N events	N at risk	Proportion	(95% CI**)	Source	N events	N at risk	Proportion	(95% CI**)	Source
	Pneumonitis grade 3/4					*Oesophagitis grade* 3/4				
CRT	2	867	0.0023	(0.0003–0.0083)	[30,32,33,35–37,40]	1	831	0.0012	(0.0000–0.0067)	[30,32,33,35–37,40]
SBRT	16	800	0.0200	(0.0115–0.0323)	[21,23,41–44,46,47,49]	2	840	0.0024	(0.0003–0.0086)	[21,23,41–44,46–49]
Protons	1	126	0.0079	(0.0002–0.0434)	[51–53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	3	210	0.0143	(0.0030–0.0412)	[55–57]	nr	nr	-	-	
	Irreversible dyspnoea grade 3/4					*Treatment-related death* (*grade* 5)				
CRT	5	980	0.0051	(0.0017–0.0119)	[30–33,35–37,40]	1	980	0.0010	(0.0000–0.0057)	[30–33,35–37,40]
SBRT	6	769	0.0078	(0.0029–0.0169)	[21,23,42–44,46,47,49]	6	870	0.0069	(0.0025–0.0150)	[21,23,41–44,46–49]
Protons	0	58	0.0000	(0.0620)	[52,53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	0	210	0.0000	(0.0170)	[55–57]	0	210	0.0000	(0.0170)	[55–57]

A B S T R A C T

Purpose: To provide a comparison between radiotherapy with photons, protons and carbon-ions in the treatment of Non-Small-Cell Lung Cancer (NSCLC), performing a meta-analysis of observational studies. *Methods:* Eligible studies on conventional radiotherapy (CRT), stereotactic radiotherapy (SBRT), concurrent chemoradiation (CCR), proton therapy and carbon-ion therapy were searched through a systematic review. To obtain pooled estimates of 2- and 5-year disease-specific and overall survival and the occurrence of severe adverse events for each treatment modality, a random effects meta-analysis was carried out. Pooled estimates were corrected for effect modifiers. *Results:* Corrected pooled estimates for 2-year overall survival in stage I inoperable NSCLC ranged from 53% for CRT to 74% for carbon-ion therapy. Five-year overall survival for CRT (20%) was statistically significantly lower than that for SBRT (42%), proton therapy (40%) and carbon-ion therapy (42%). However, caution is warranted due to the limited number of patients and limited length of follow-up of the particle studies. *Conclusion:* Survival rates for particle therapy were higher than those for CRT, but similar to SBRT in stage I inoperable NSCLC. Particle therapy may be more beneficial in stage III NSCLC, especially in reducing adverse events.

 Radiotherapy and Oncology 95 (2010) 32–40

* Radiotherapy with high-energy charged particles has become an attractive therapeutic option for patients with several tumour types because this approach better spares healthy tissue from radiation than conventional photon therapy. The cost associated with the delivery of charged particles, however, is higher than that of even the most elaborate photon-delivery technologies. Reliable evidence of the relative cost-effectiveness of both modalities can only come from the results of randomized clinical trials. Thus, the hurdles that currently limit direct comparisons of these two approaches in clinical trials, especially those related to insurance coverage, should be removed. Herein, we review several randomized trials of charged-particle therapies that are ongoing, with results that will enable selective delivery to patients who are most likely to benefit from them. We also discuss aspects related to radiobiology, including the immune response and hypoxia, which will need to be taken into consideration in future randomized trials to fully exploit the potential of charged particles.

* Charged-particle therapy in cancer: clinical uses and future perspectives

Key points

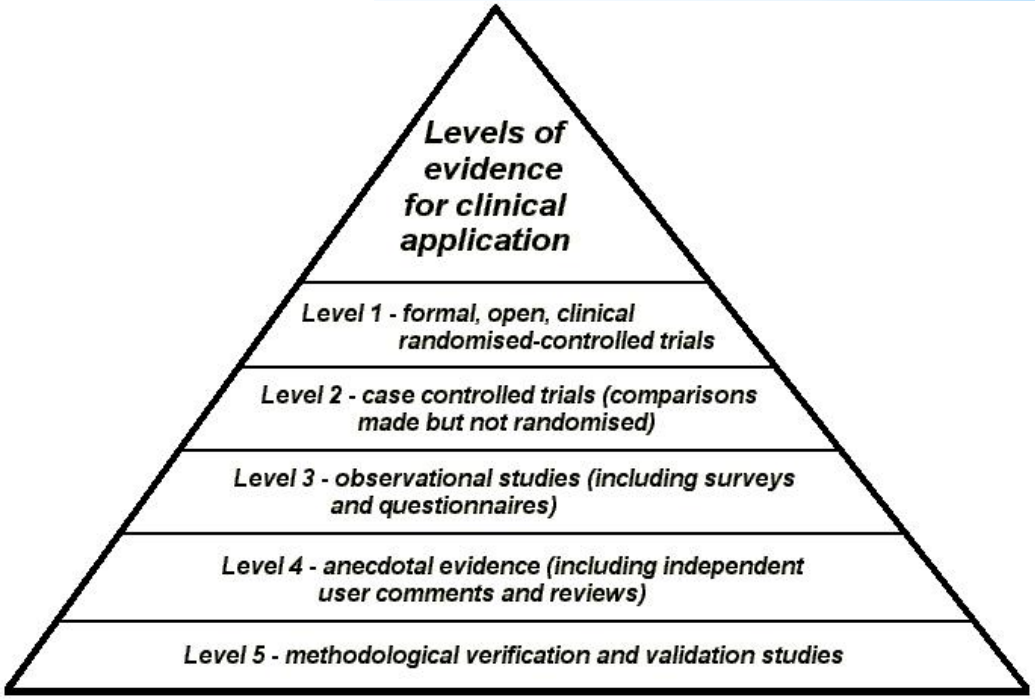
- Owing to their physical properties, the therapeutic use of charged particles in radiotherapy is advantageous over photon-based radiotherapy
- The delivery of charged particles is more costly than that of X-rays, with no level 1 evidence currently indicating clinical superiority of either approach
- Randomized trials are essential to establish the clinical benefit derived from charged-particle therapy; several studies are currently ongoing worldwide
- The design of clinical trials for the comparison of different radiotherapy modalities is very complex; careful patient selection is essential to obtaining meaningful results
- The criteria for patient selection for radiotherapy trials need to take dosimetric and radiobiological considerations into account

Table 1. Levels of Evidence Provided by Different Study Types[a]

Level of Evidence	Study Type
1	High-quality, properly powered and conducted RCT; systematic review or meta-analysis of these studies
2	Well-designed controlled trial without randomization; prospective comparative cohort trial
3	Retrospective cohort study, case-control study, or systematic review of these studies
4	Case series with or without intervention; cross-sectional study
5	Expert opinion, case report, or bench research

Abbreviation: RCT, randomized clinical trial.

[a] Adapted from Oxford Centre for Evidence-Based Medic (http://www.cebm.net/2011-oxford-cebm-levels-evidence-i



* charged particles, which include protons and heavy ions (typically carbon).
* approximately two-thirds of patients with cancer who are treated with radiotherapy
  * >80% receive X-rays vs. ~0.8% receive radiation from high-energy charged particles
* FIG.1: gegraphical distribution of CPT

* Charged-particle therapy in cancer: clinical uses and future perspectives

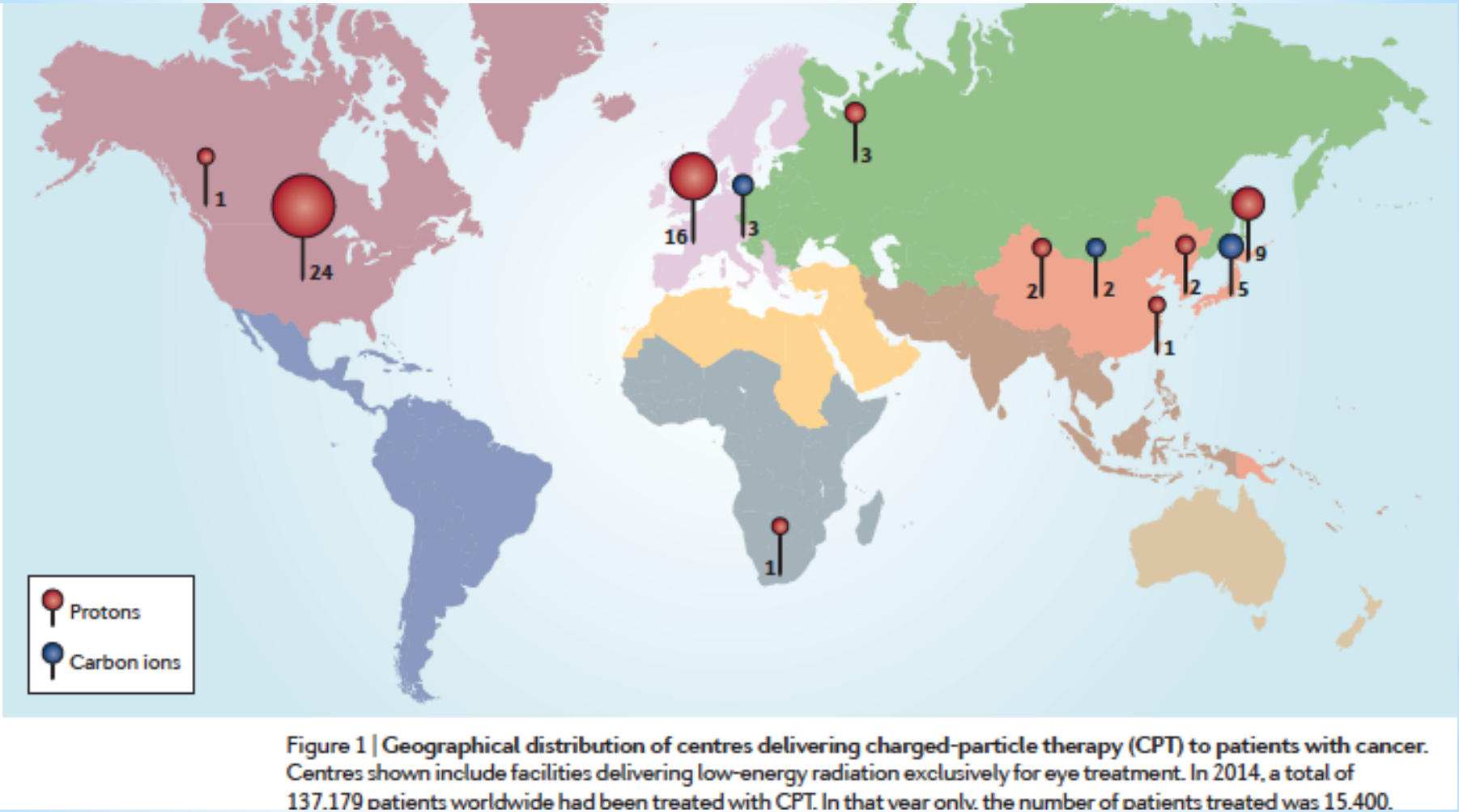
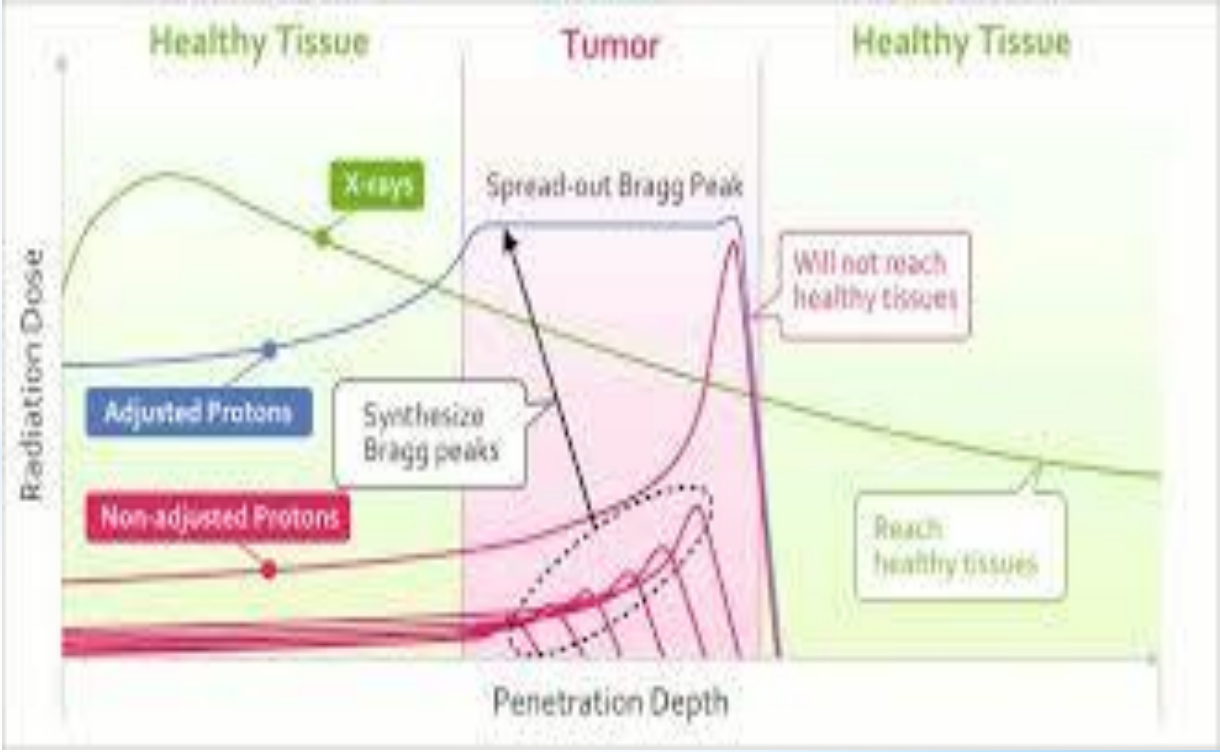


Figure 1 | Geographical distribution of centres delivering charged-particle therapy (CPT) to patients with cancer. Centres shown include facilities delivering low-energy radiation exclusively for eye treatment. In 2014, a total of 137,179 patients worldwide had been treated with CPT. In that year only, the number of patients treated was 15,400.

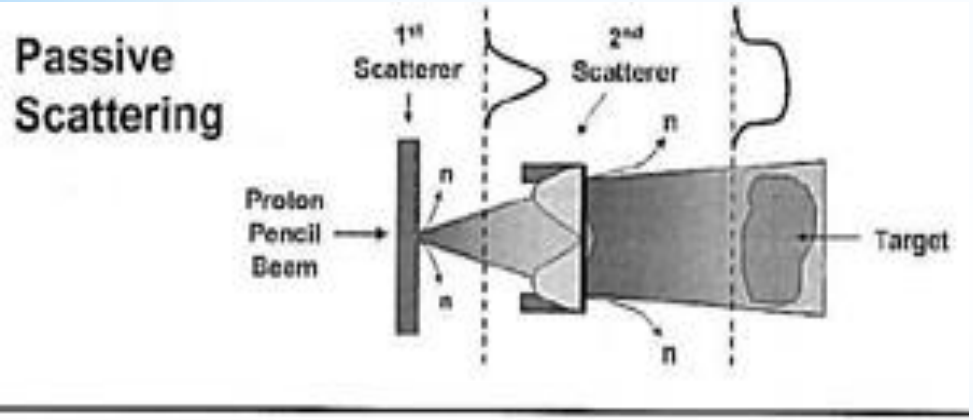
* CPT energy deposited per unit track increases with depth reaching a sharp & narrow maximum peak close to the end of the range, Bragg Peak (BP)
* CPT lower dose to none-malignant normal tissue(s) & OAR (organs at risk)

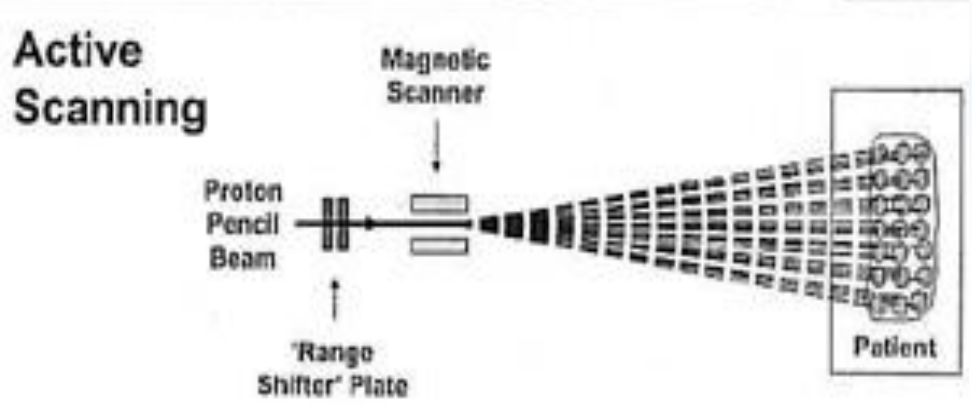


To cover the 3D geometry of a tumor the BP has to be widened: spread out Bragg Peak (SOBP)

SOBP is achieved by:

- Passive scattering of monoenergetic beam
- PBS: pencil beam scanning
- IMPT: intensity modulated proton therapy





Passive scattering

Passive scattering is a dose-delivery system in particle therapy in which a broad monoenergetic beam is used to treat a tumour. The energy variation is obtained with compensating filters of different depths and the shape is controlled with patient-specific collimators.

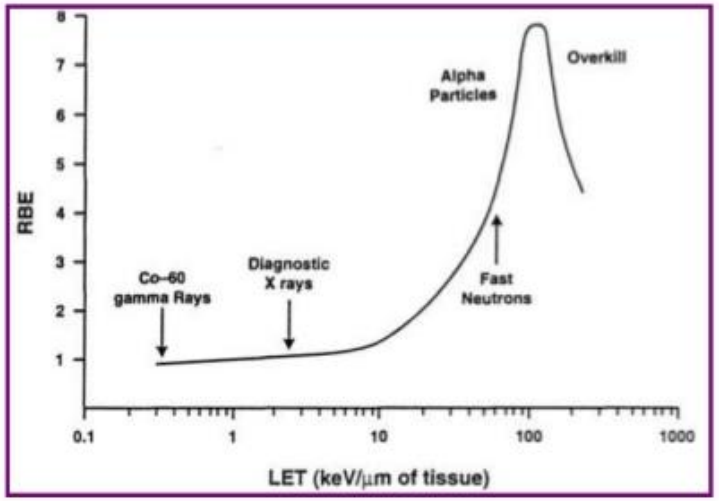
Pencil-beam scanning

Pencil-beam scanning (PBS) is a dose-delivery system in particle therapy in which the beam is concentrated in spots of a few millimeters of diameter, and scanned through a 2D tumour slice. By changing the energy, a new slice can be scanned.

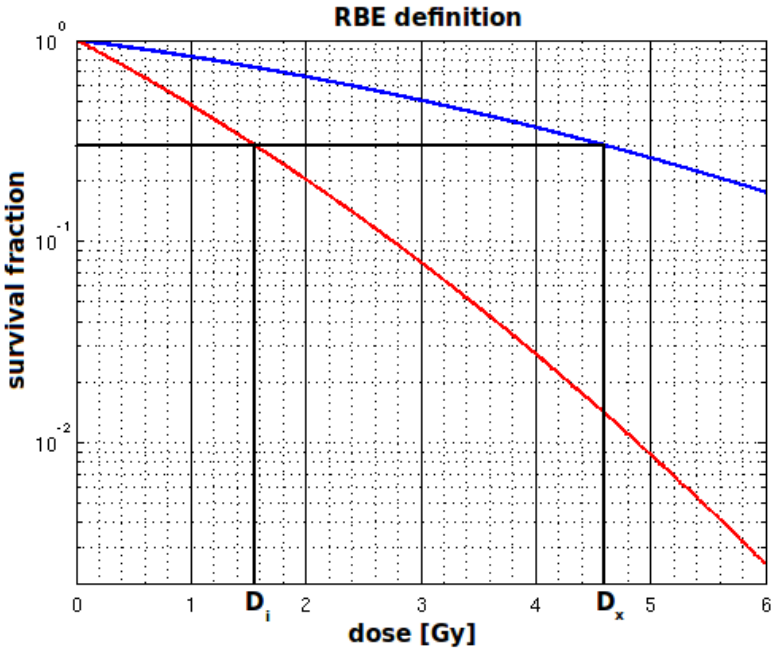
Intensity-modulated proton therapy

Intensity-modulated proton therapy (IMPT) is a dose-delivery system in proton therapy in which the intensity of each pencil beam is modified to achieve a better target coverage. Intensity modulation is also used in X-ray-therapy.

RBE
relative biological effectiveness: ratio of biological effectiveness of one type of ionizing radiation relative to another, given the same amount of absorbed energy



In the case of sparsely ionizing X-rays the probability of a single track causing a DSB is low, thus X-rays have a low RBE. At the other extreme, densely ionizing radiations (ex. LET of 200 keV/ μm) readily produce DSB, but energy is "wasted" because the ionizing events are too close together. Thus, RBE is lower than optimal LET radiation.



Relative biological effectiveness. Protons are light particles and their RBE is low, except at the end of the particle range in the tissue. The LET of protons is ~1 keV/μm in the entrance channel, similar to that of X-rays, and increases up to 2–6 keV/μm in the SOBP[3]. In clinical practice, a fixed RBE value of 1.1 is used[79], a choice that is certainly not correct, because RBE changes along the Bragg curve. Over the past decade many investigators have

of radioresistant tumours. The dose distribution of carbon ions is slightly better than that of protons owing to reduced lateral scattering of heavier ions[3]. In addition, carbon ions accelerated at therapeutic energies (200–400 MeV/n) have a LET in the entrance channel of 11–13 keV/μm, and a fairly high LET on the SOBP (40–90 keV/μm). Such LETs differentiate the therapeutic properties of carbon ions from those of X-rays or protons — similar to differences between drugs.

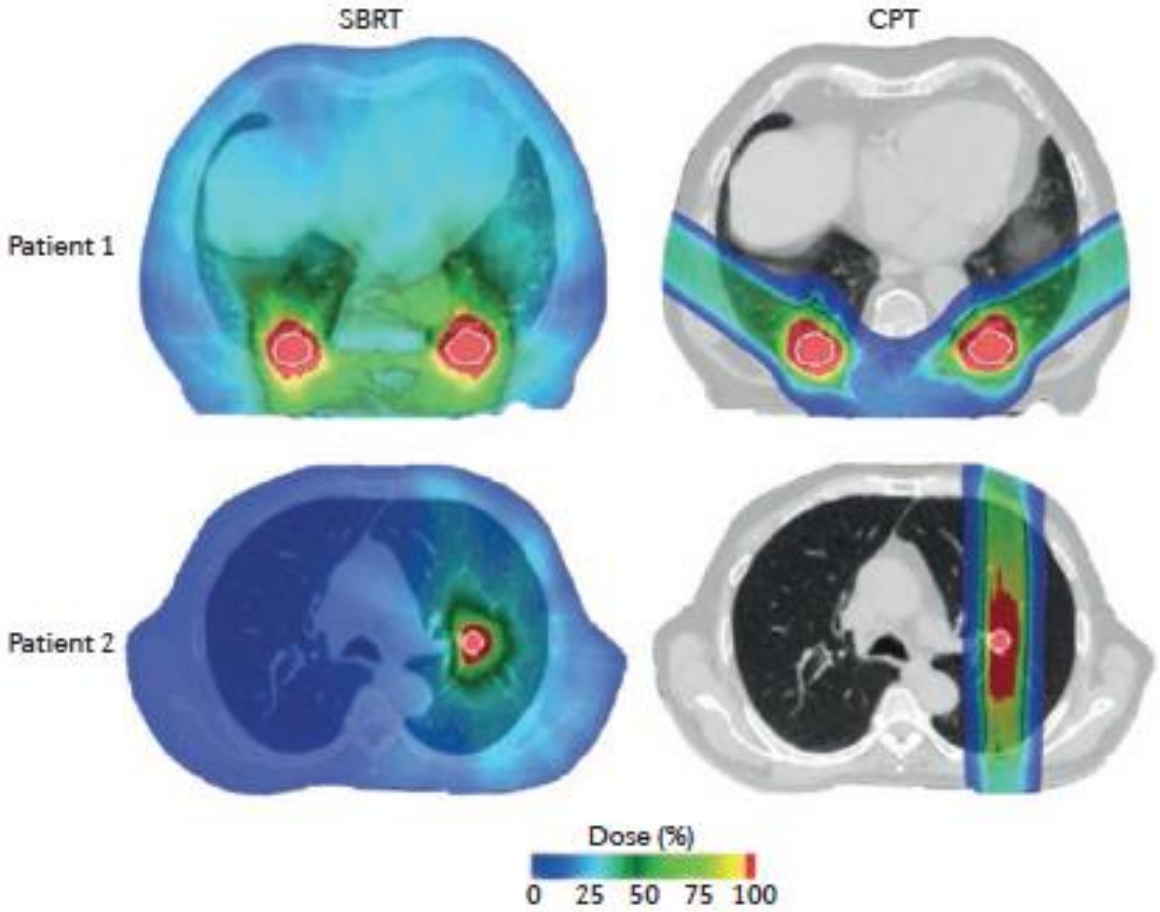
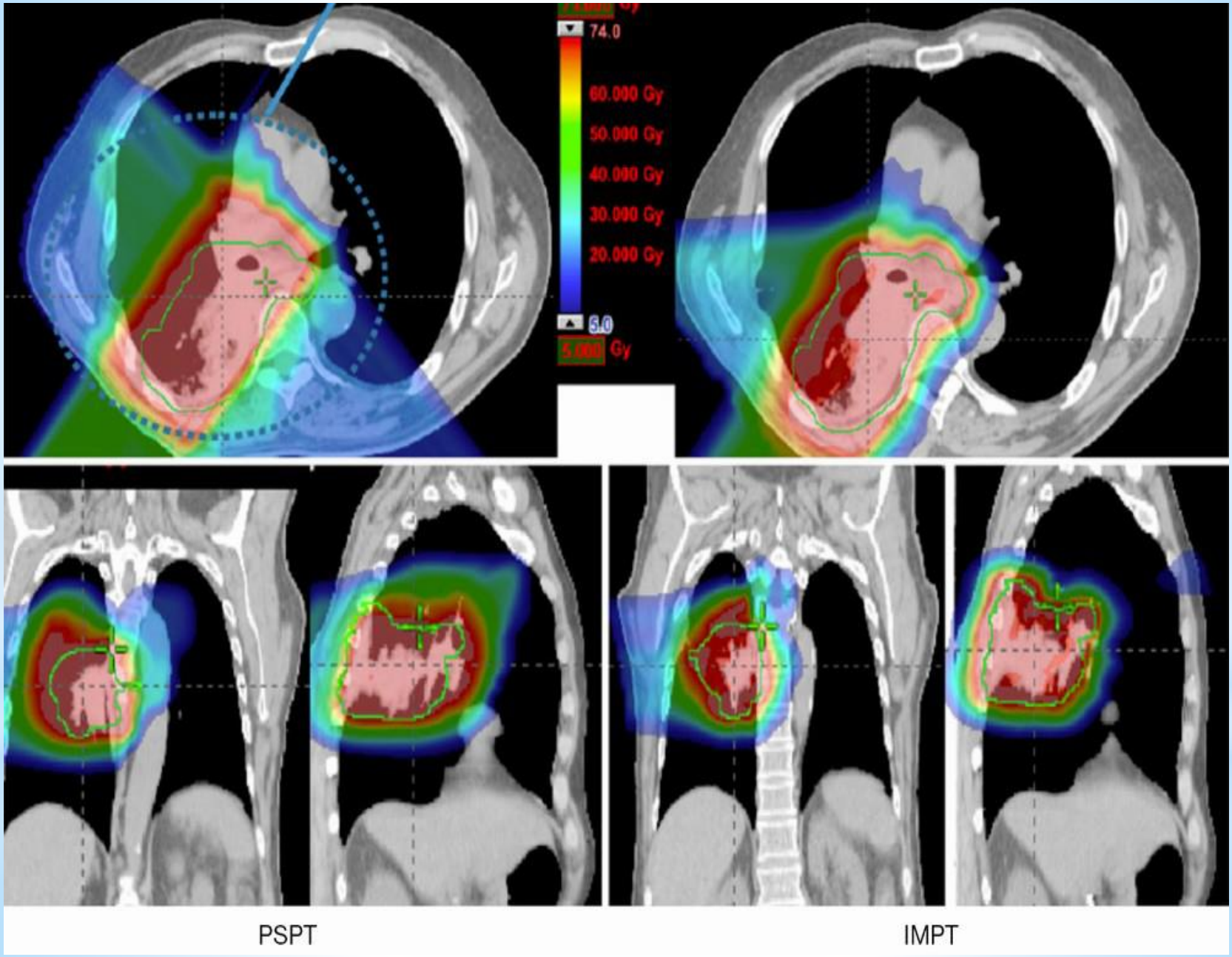
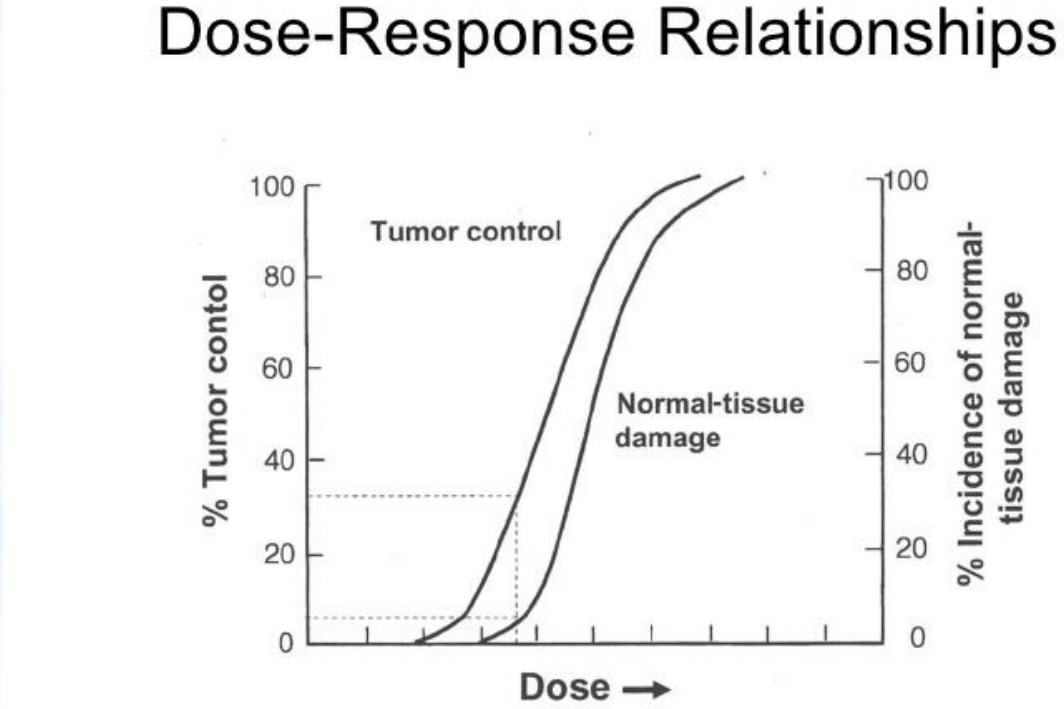


Figure 4 | **Treatment plans using stereotactic body radiotherapy (SBRT) or charged-particle therapy (CPT) for two patients with NSCLC.** Patient one is more likely to benefit from CPT than from SBRT owing to the large integral dose necessary to treat multiple lesions with X-rays. Conversely, patient two is more likely to benefit from SBRT than from CPT owing to the small size of the lesion (1.6 cm^3) and its location in a central region of the lung, which would result in a larger planning target volume (PTV) with CPT than with SBRT (32 cm^3 versus 7.7 cm^3). The clinical target volume contour is outlined in white. Image part of an *in silico* trial for comparison of SBRT and CPT with carbon ions[72], modified from Anderle, K. *et al. In silico* comparison of photons versus carbon ions in single fraction therapy of lung cancer. *Phys. Medica* 32, 1118–1123 (2016), with permission from Elsevier.


74.0
60.000 Gy
50.000 Gy
40.000 Gy
30.000 Gy
20.000 Gy
5.0
5.000 Gy
PSPT
IMPT

* With CPT a given tumor radiation dose (TCP: tumor control probability) can be achieved at lower integral dose to nonmalignant tissue(s) and OAR (reducing NTCP: normal tissue complication probability)



COST		
Photon/Linac	*Single room Proton*	*X rooms Protons*
$5.000.000	$20.000.000	$200.000.000
	CPT cost/treatment ~ 3x > photon therapy	
	Cost benefit ratio remains CONTROVERSIAL without Level 1 evidence of superiority to photon therapy	
	Data from well designed RCTs are needed	

Clinical Trials

* Challenges:
  * Superiority of CPT based on outcomes: morbidity (treatment related toxicity), QOL(quality of life) requiring long follow-ups and surveillance…cost
  * Ethics: access, pediatrics
  * Insurance coverage: access to CPT
  * Limited # CPT centers: patients QOL: travel/accommodations
  * Different beam-delivery technologies: PS vs. PB

* aa

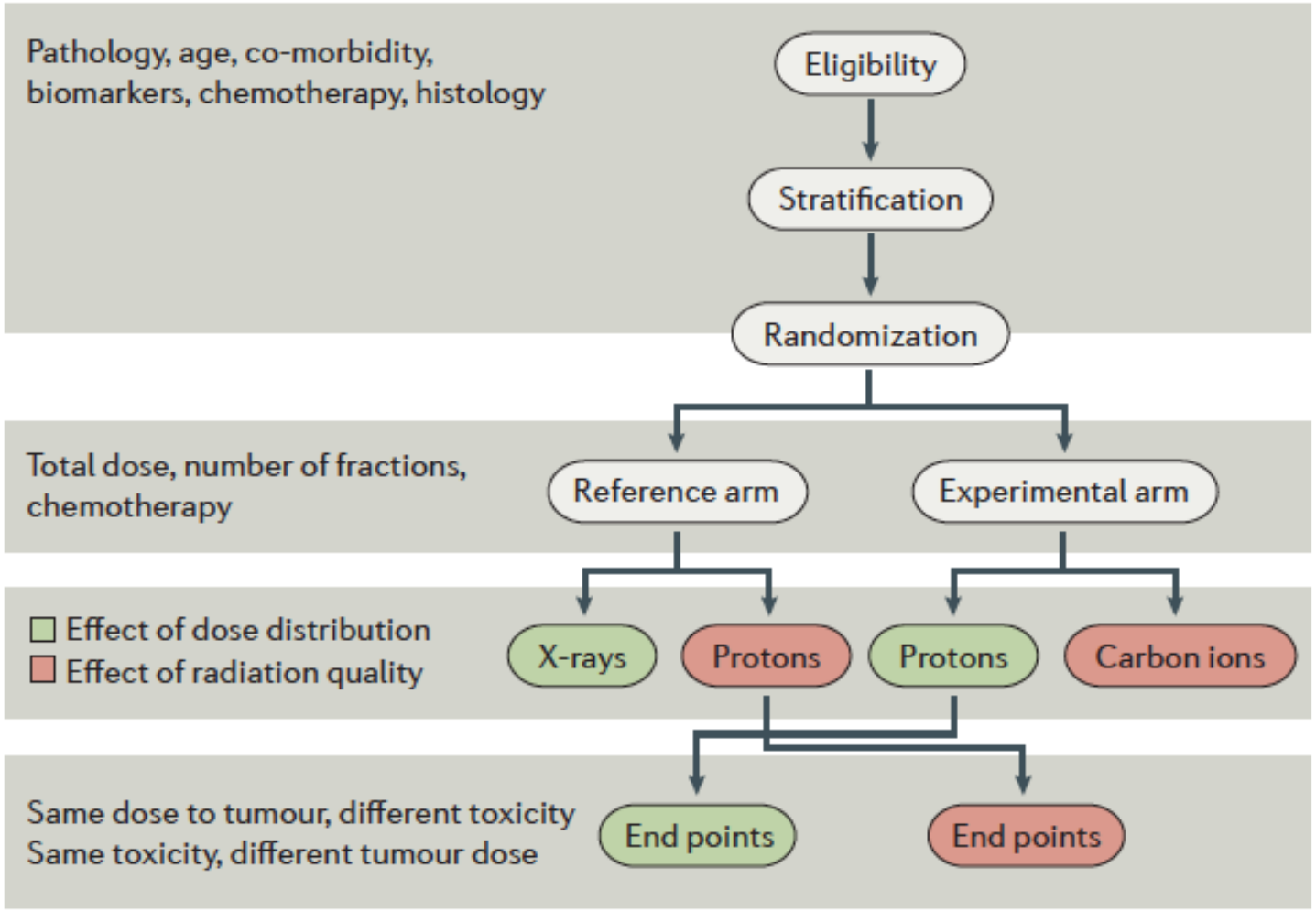


Figure 3 | **Clinical trial design in charged-particle therapy (CPT).** General procedure in CPT trials: patients in the control arm generally receive X-rays, unless the aim of the trial is to compare different charged particles (for example, protons versus carbon ions). Trials of X-rays versus protons or carbon ions compare different physical dose-distributions and the end point can be decreased toxicity (if the same dose to tumour is prescribed), or increased local disease control (if trials prescribe isotoxic doses). Trials comparing protons to carbon ions will have similar physical dose-distribution, and the main end point will be the effect of biological effectiveness.

Table 1 | Ongoing randomized clinical trials comparing different radiation modalities for the same disease

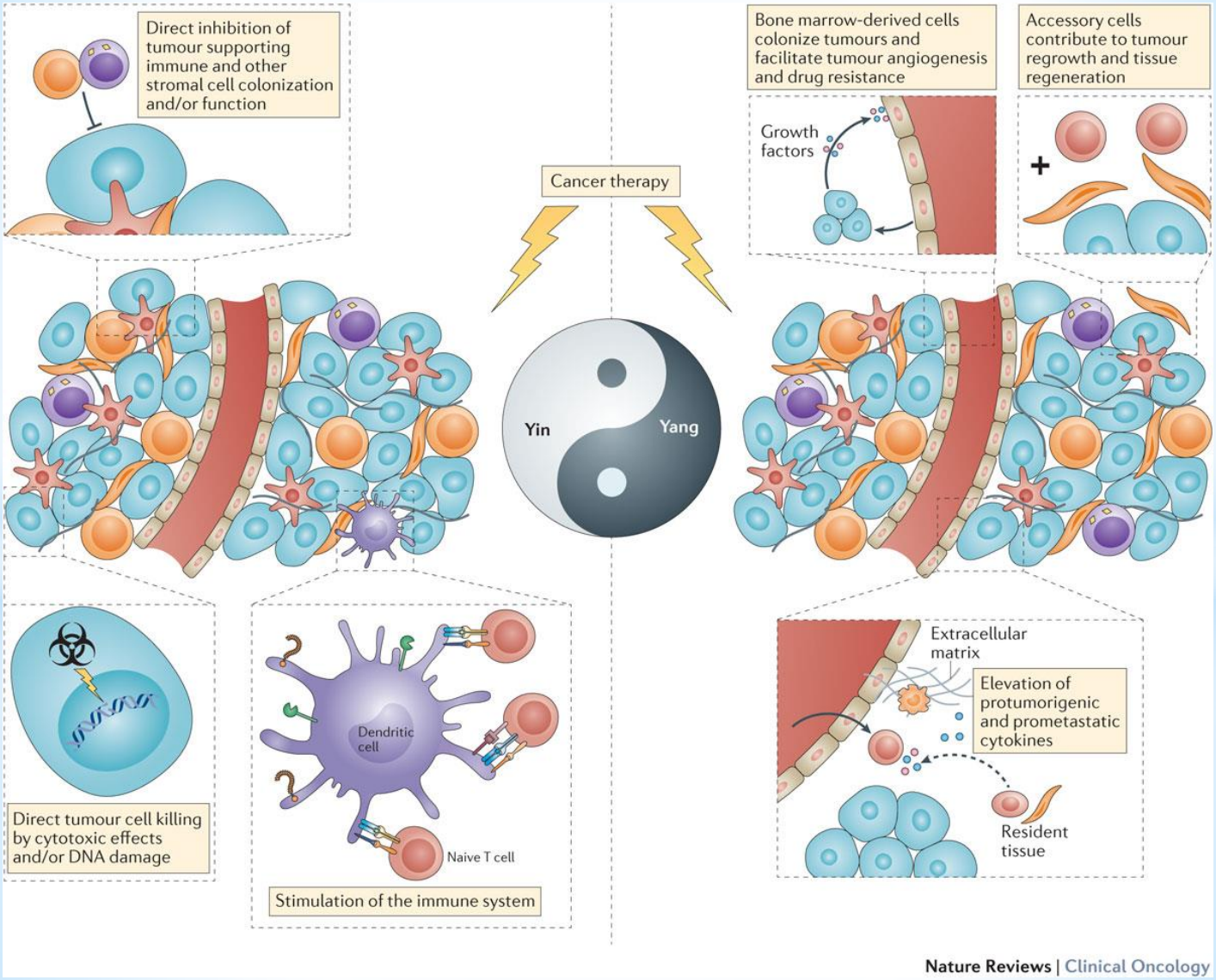
Study	Institution	Phase	Condition	Radiation arm 1	Radiation arm 2
R03CA188162: IMPT vs IMRT	MDACC	III	Oropharyngeal cancer (head and neck cancer)	Protons*	X-rays*
PARTIQoL (NCT01617161): proton therapy vs IMRT	MGH	III	Low-risk or intermediate-risk prostate cancer	Protons	X-rays
NCT01512589: proton-beam therapy vs IMRT	MDACC	III	Oesophageal cancer	Protons*	X-rays*
RADCOMP (NCT02603341): pragmatic randomized trial of proton vs photon therapy	PTCORI	III	Post-mastectomy stage II or III breast cancer	Protons	X-rays
NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation	NRG Oncology	II	Newly diagnosed glioblastoma	Protons*	X-rays*
NRG 1542: proton radiation vs conventional photon radiation‡	NRG Oncology	III	Hepatocellular carcinoma	Protons	X-rays
NCT01182753: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Low-grade and intermediate-grade chondrosarcoma of the skull base	Protons	Carbon ions
NCT01182779: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	Carbon ions
CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Primary glioblastoma	Protons*§	Carbon ions*§
IPI (NCT01641185): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Prostate cancer	Protons	Carbon ions
ISAC (NCT01811394): proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	Carbon ions
ETOILE (NCT02838602): carbon-ion radiotherapy vs IMRT	Lyon University Hospital, France	III	Radioresistant adenoid cystic carcinoma and sarcomas	Carbon ions	IMRT
BAA-N01CM51007-51: prospective trial of carbon-ion therapy vs IMRT	NCI	I/III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*
CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy	UTSW	III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*

IMPT, intensity modulated proton therapy; IMRT, intensity modulated radiation therapy (X-rays); MDACC, MD Anderson Cancer Center (Houston, Texas, USA); MGH, Massachusetts General Hospital (Boston, Massachusetts, USA); NCI, US National Cancer Institute (Bethesda, Maryland, USA); PTCORI, Patient-Centered Outcomes Research Institute (University of Pennsylvania, USA); UTSW, University of Texas Southwestern Medical Center (Dallas, Texas, USA). *In combination with chemotherapy. ‡Trial not yet registered. §Boost following conventional chemoradiotherapy.

Radioimmunotherapy. The combination of radiotherapy with immunotherapy, to convert the individual tumour into an '*in situ* vaccine', is currently considered one of the most promising strategies to defeat cancer[104,105]. Radiation can induce both immunostimulatory and immunosuppressive pathways, depending on the activation of different cell-death pathways[106]. While immunotherapy can block immunosuppressive pathways, the effect of radiation from heavy ions on cell-death signalling can elicit a more generalized immune response compared with that observed with photon-based therapy[107]. This hypothesis is supported by the strong abscopal effect observed in patients treated with radiation from high-LET particles[108],

Radioresistant/Hypoxic tumors:
Hit & ETOILE trials

Figure 1 The tumour promoting and inhibitory effects of anticancer agents: Yin and Yang effects



Shaked, Y. (2016) Balancing efficacy of and host immune responses to cancer therapy: the yin and yang effects
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.57

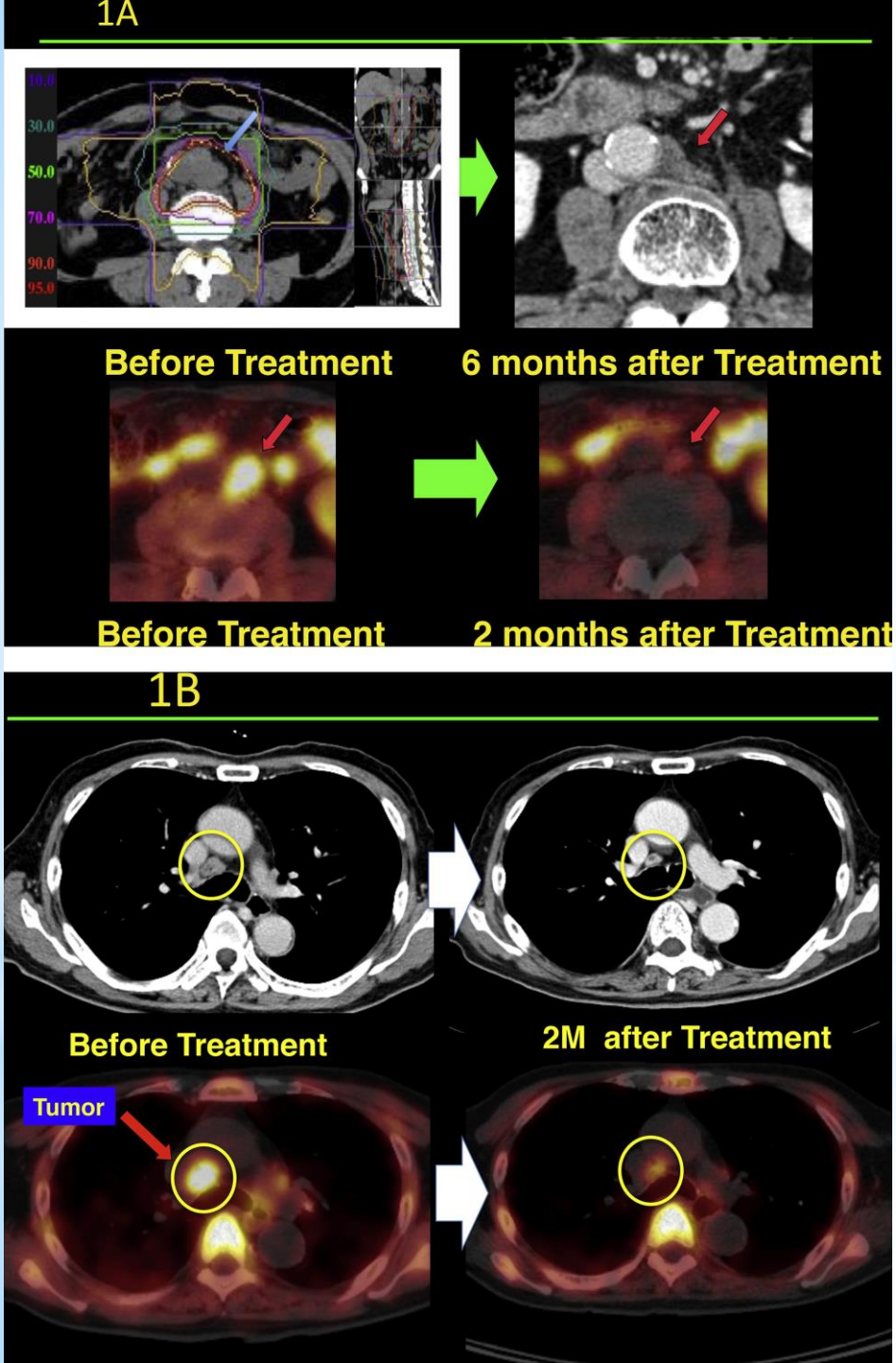
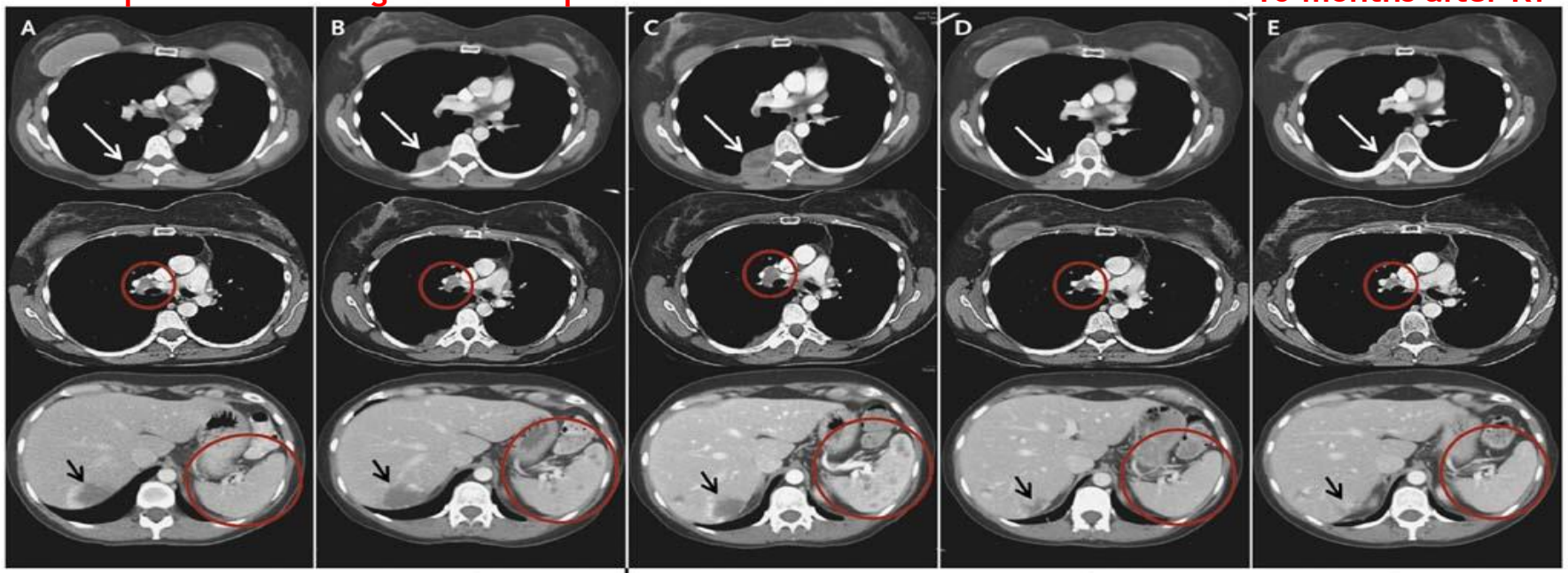


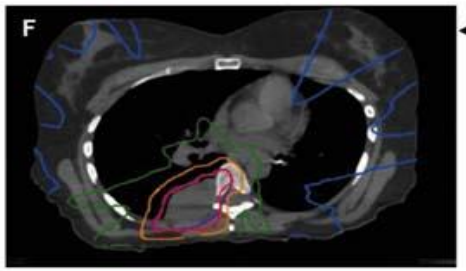
Fig. 1. An 85-year-old patient received 50.4 GyE in 12 fractions for an ascending colon carcinoma at National Institute of Radiological Sciences, Chiba, Japan (A). At the time of treatment the patient had mediastinal lymph node metastasis, at computed tomography and methionine positron emission tomography imaging (B). Six months after treatment, resolution of both the irradiated lesion (A) and the metastasis occurred (B).

Courtesy of Dr Shigeru Yamada

Durante, M., Brenner, D. J. & Formenti, S. C. Does heavy ion therapy work through the immune system? *Int. J. Radiat. Oncol. Biol. Phys.* **96**, 934–936 (2016).

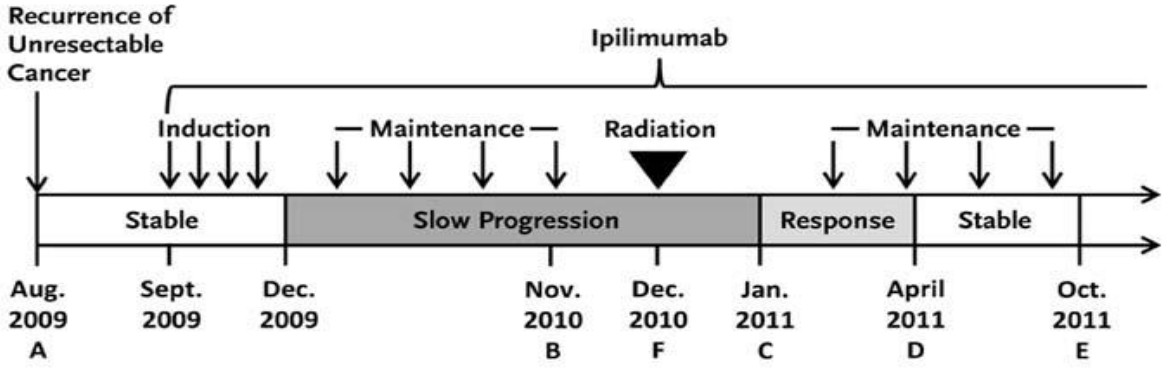
Abscopal Effect





December 2010

9.5 Gy x 3 f



Postow et al. *N Engl J Med* 366:925-31, 2012

Conclusions

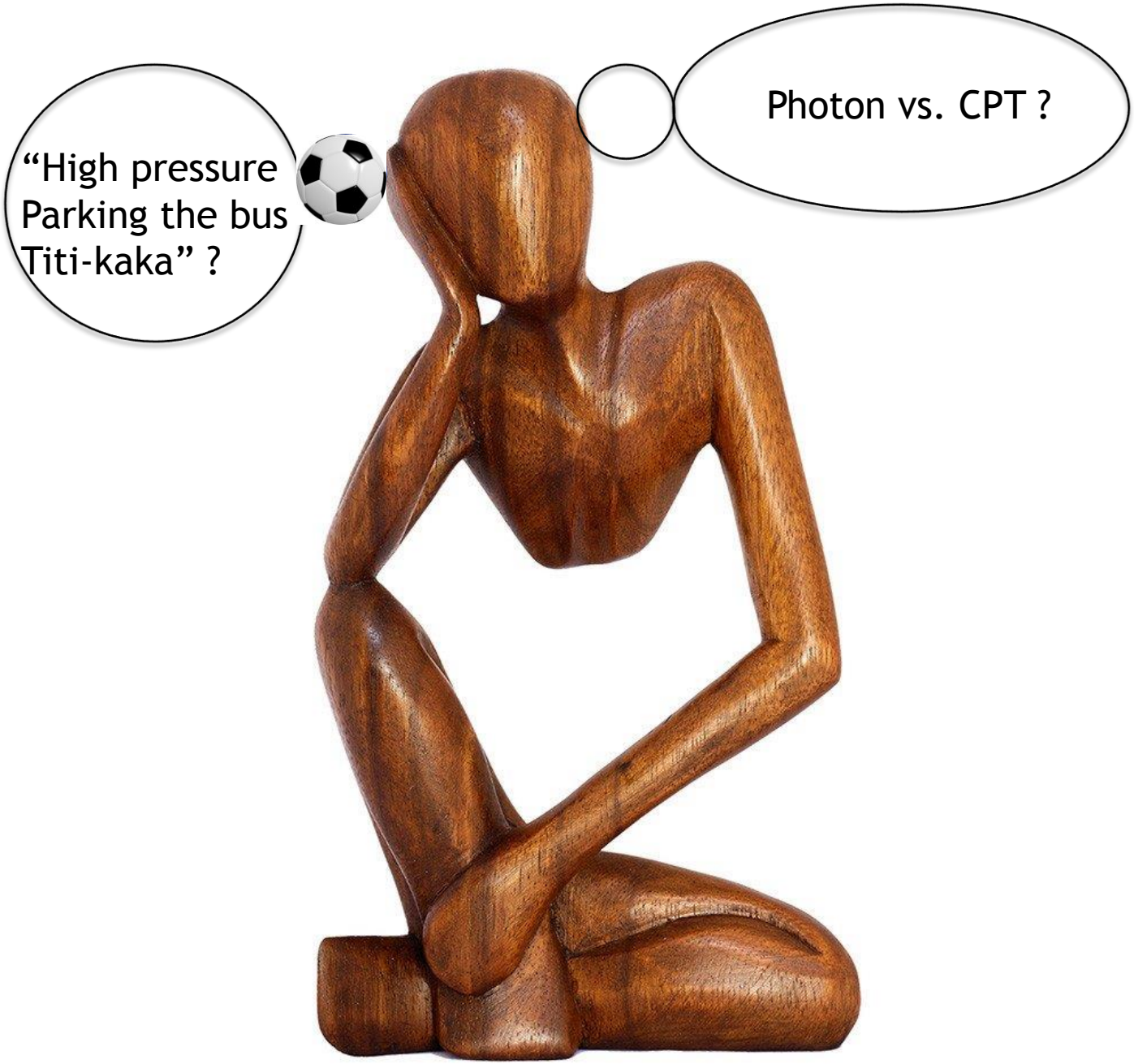
Centres delivering proton therapy are rapidly being created in many regions. The delivery of heavy-ion therapy is also expanding, with solid plans for making this modality available in the USA[125,126]. A lack of level 1 evidence exists regarding the superiority of CPT over X-ray irradiation — a paucity that is likely to be solved with the publication of results from the many ongoing randomized clinical trials (TABLE 1). The costs associated with CPT delivery have been decreasing, and single-room solutions now cost $20–40 million, compared with $100 million a few years ago; however, and despite the introduction of CPT >20 years ago, the issue of cost-effectiveness remains to be solved. The cost of CPT is higher than that associated with X-ray therapies and, even if such costs are decreasing, substantial changes are not likely to occur. Finally, we have discussed that the use of toxicity as the end point in clinical trials might lead to a lack of statistically significant results and, as noted by Bentzen[16], to a requirement to perform phase IV radiovigilance studies.

The construction of new treatment centres raises the question of how many centres are needed to treat patients who can potentially benefit from CPT. The established indications for which the advantage of using charged particles is well-established (for example, ocular tumours or chordomas of the skull base) relate to only 1–2% of patients with cancer, but with the inclusion of other patient populations in clinical trials this fraction could rise to 15–20%; different eligibility criteria for CPT are currently used or under evaluation in different countries[3,127]. In reality, however, the clinical benefit derived by patients should be evaluated on an individual basis, which is an achievable task. At present, patient cohorts in CPT trials belong to one of three models: trials in which comparisons between cohorts are hardly possible (such as those for paediatric cancer), randomized trials without patient selection; and randomized trials in which patients are selected using biomarkers (including hypoxia), dosimetry, or NTCP models[76]. The latter model-based approach is complicated, but is also evidence-based, intrinsically includes a control cohort, and can be amended over time. These patient selection models should be encouraged and used when determining the number of facilities delivering CPT that are required in a specific geographical area.

A bench-to-bedside translational approach is well-suited for CPT studies; the results from large-sized preclinical radiobiology research studies should form the basis for the design of clinical trials. For proton-based therapies, the usefulness of RBE models in treatment planning for reducing the dose to the normal tissue should be tested. Therapies with heavier ions seem to be advantageous for the treatment of hypoxic tumours, especially in combination with immunotherapy.

Our ability to conduct comparative phase III trials of CPT is currently obstructed by hurdles, such as insurance coverage[128] — which should be firmly addressed with third parties because the potential benefit from CPT is very high. A balanced approach needs to be taken when planning the construction of new centres delivering CPT; importantly, the associated costs should be taken into account. In large-volume centres (such as those currently under construction in Austria and South Korea, or planned in the USA), different ions should be delivered, a strategy that will enable the much needed comparative trials to take place, especially those including hypofractionation and/or treatment combinations.

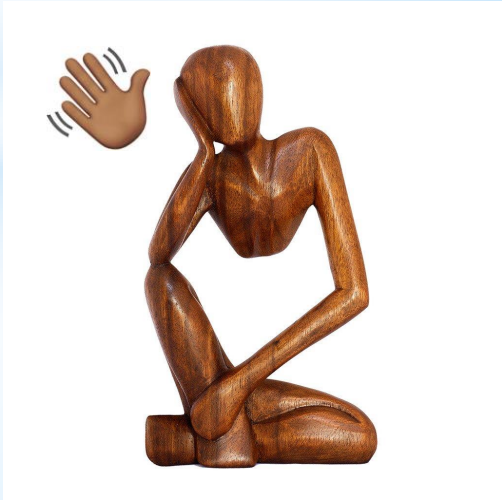

What ‘s a man to do?


“High pressure
Parking the bus
Titi-kaka” ?
Photon vs. CPT ?


May the best team win !

*?

*Thank you



Medical Physics Unit - McGill University

https://www.mcgill.ca/medphys/

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Medical Physics Student Council. From left to right: Marc-André ...

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Fax: 514-934-8229
Email: margery.knewstubb@mcgill.ca
Website: www.mcgill.ca/medphys

About Medical Physics

The Medical Physics Unit is a teaching and research unit concerned with the application of physics and related sciences in medicine, especially (but not exclusively) in radiation medicine; i.e., radiation oncology, medical imaging, and nuclear medicine. The Unit offers an M.Sc. in Medical Radiation Physics. Facilities are available for students to undertake a Ph.D. in Physics administered through the Department of Physics with a research emphasis on medical physics supervised, funded, and hosted by Medical Physics Unit PI's (principal investigators). Facilities are also available for students to undertake a Ph.D. in Biological and Biomedical Engineering administered through the Departments of Biomedical Engineering and Bioengineering with a research emphasis on medical physics and supervised, funded, and hosted by Medical Physics Unit PI's.

Medical Physics Admission Requirements and Application Procedures

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See *University Regulations & Resources* > *Graduate* > *Graduate Admissions and Application Procedures* > Application Procedures for detailed application procedures. Further information regarding the application procedures is available on the Medical Physics Unit website.

Only complete applications will be considered.

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Under **Program choice**:
"Application type" = Degree, certificate, or diploma
"Term" = Fall 2019
"Department" = Medical Physics Unit
"Program" = M.Sc. Med Radiation Physics (Thesis)
"Area of study" = Medical Radiation Physics-T
"Status" = Full Time

Under **Additional Questions**:
Please indicate source(s) of funding to cover tuition & student fees + living expenses while studying at McGill University.

Some References

* Radioprotection: slides show
  * https://slideplayer.com/slide/8396219/
* Podgorsak, E.B., *Radiation Physics for Medical Physicists, 2nd ed., 2010, XXXIII, 745 p. 190 illus., 16 in color., HardcoverISBN: 978-3-642-00874-0*
* Khan, F.M. *The Physics of Radiation Therapy, Williams & Wilkins, Baltimore*
* Hall, E.J. *Radiobiology for th*