PROTON THERAPY IN CLINICAL PRACTICE: PAST, PRESENT AND FUTURE

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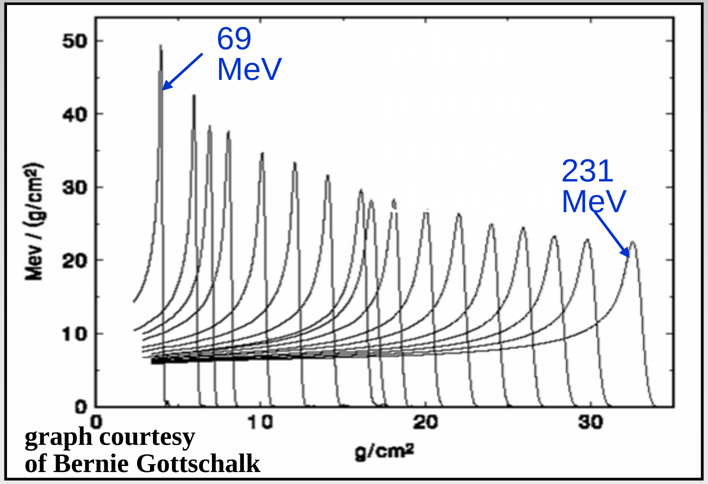
Synopsis

1. Physics
   - interactions of protons with matter
   - treatment planning
2. Technology
   - beam generation, shaping and delivery
   - patient handling
   - integration
3. Radiobiology
   - RBE
   - modelling and treatment strategy
4. Clinical Application
   - clinical experience
   - clinical trials

INTERACTIONS OF PROTONS WITH MATTER

proton penetration

ICRU (1993). Stopping Powers and Ranges for Protons and Alpha Particles, ICRU Report 49

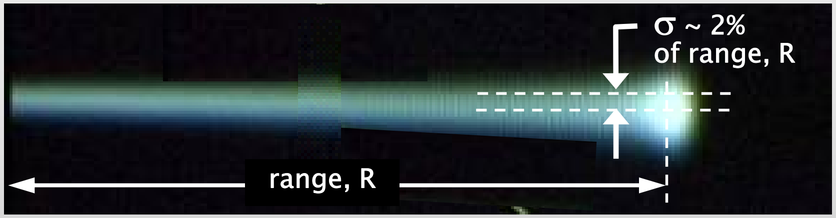


graph courtesy of Bernie Gottschalk

multiple Coulomb scattering

Gottschalk *et al.* (1993) Multiple Coulomb scattering of 160 MeV protons. Nucl Instr Methods Phys Res B74:467–490.

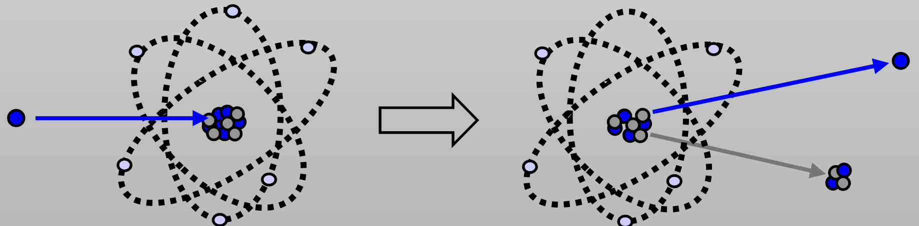
and http://huhepl.harvard.edu/~gottschalk/



Based on a figure courtesy of Eros Pedroni, PSI

nuclear interactions

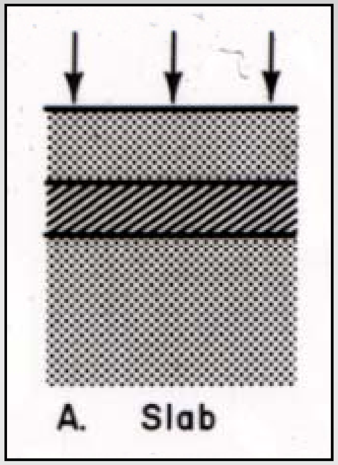
there is a vast literature

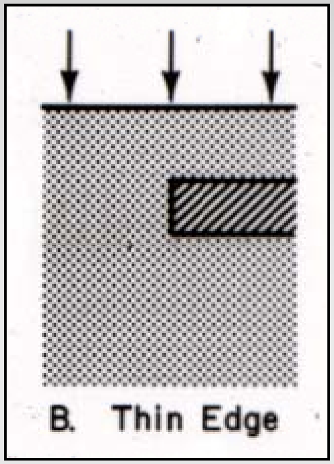


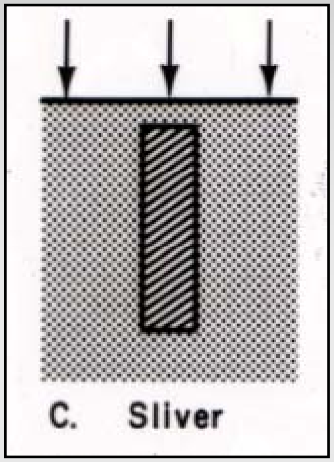
DOSIMETRY

- See ICRU report number 78
  - basically adopts IAEA's prior protocol (TRS 398) (thus eliminating a 2% discrepancy)
  - proton dosimetry is based on X-ray calibration of ion chambers, with correction factors
  - however, the largest correction factor is in the w-value of protons in the ion chamber gas, and this value largely relies on Calorimetric determinations
- Stated standard error of from 2.0% to 2.3%
- Most important point:
  - Proton dosimetry is now standardized and the standard is (or will soon be) near-universally followed

INHOMOGENEITIES

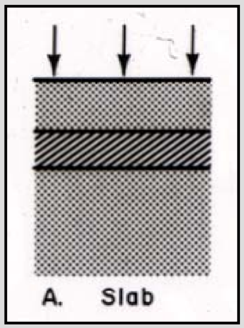


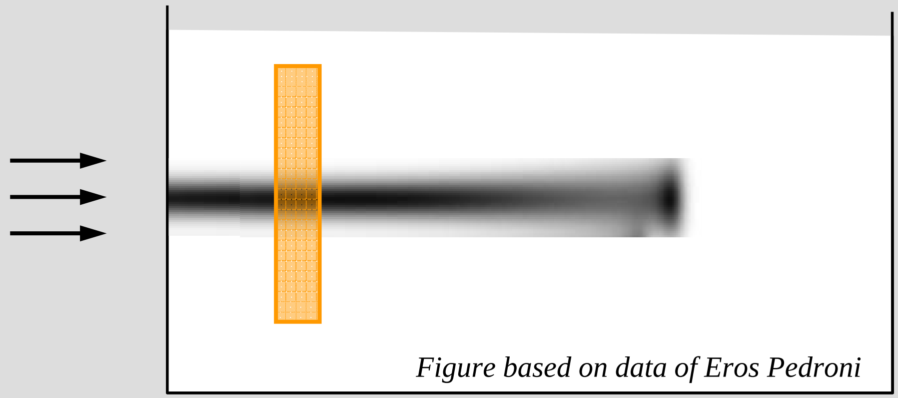


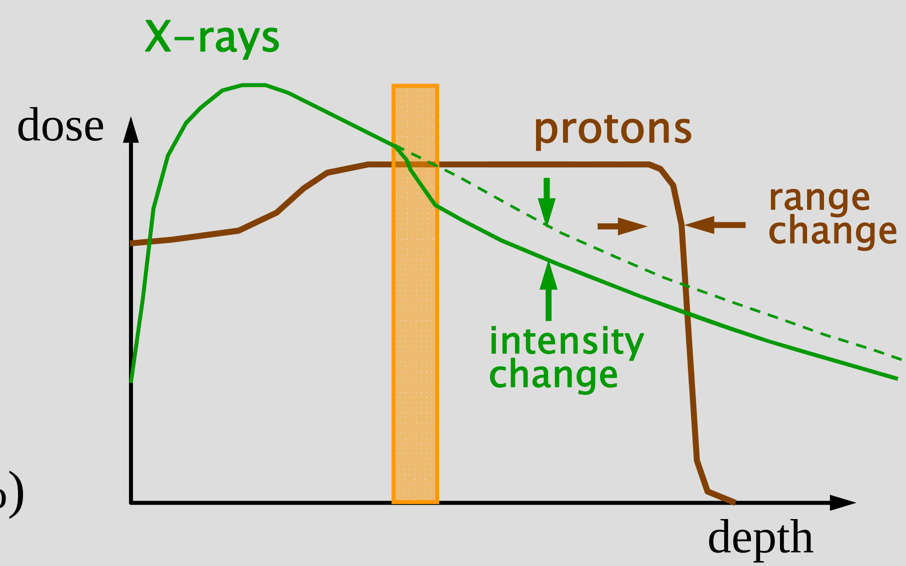


and

INFINITE SLAB

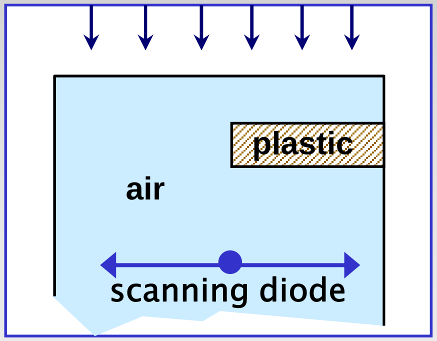




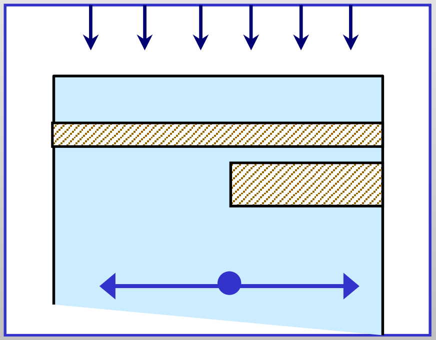


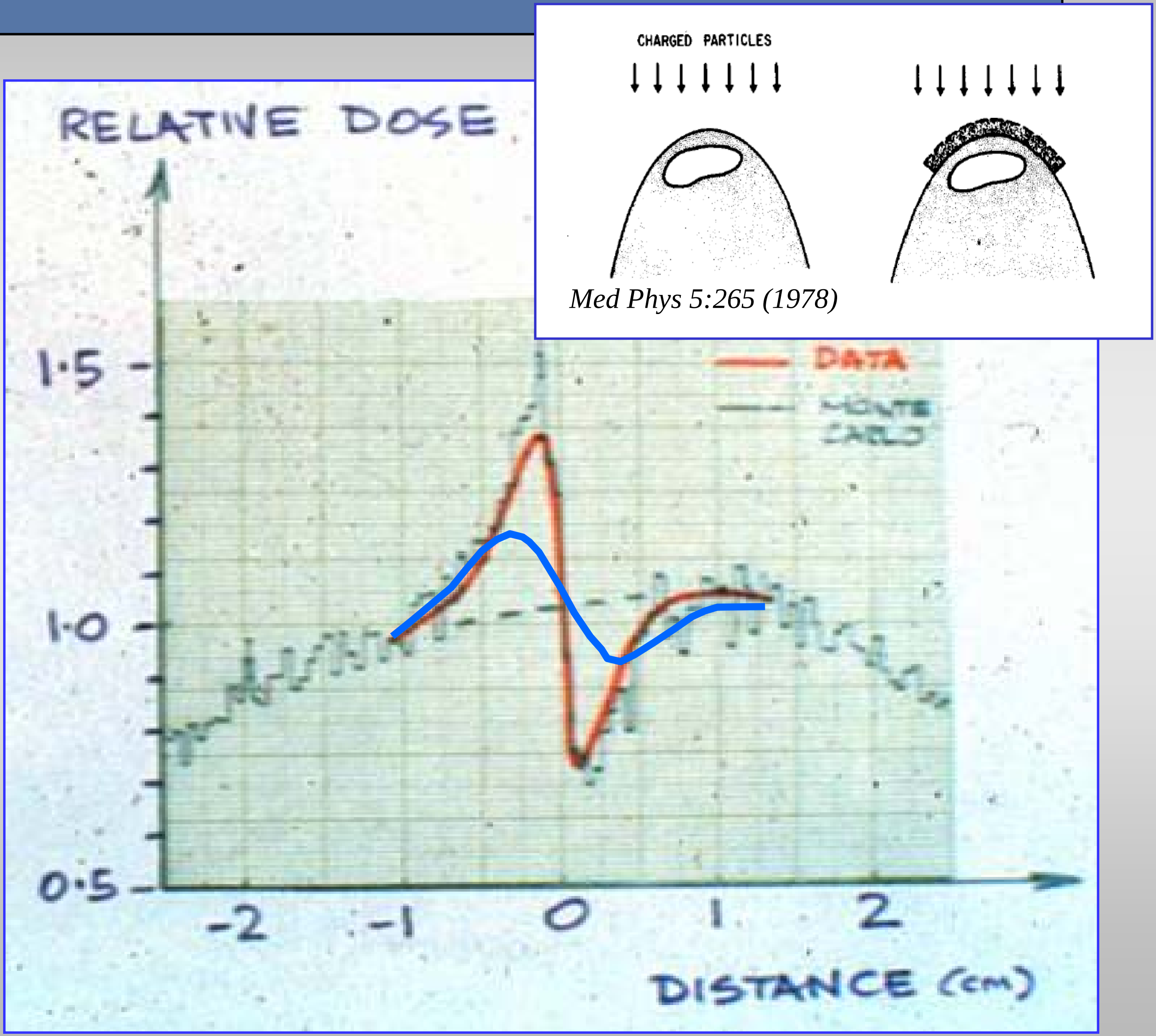
interface effects are minor (few %)
– *Koehler (unpublished)*

SEMI-INFINITE SLAB (thin edge)



overlying material



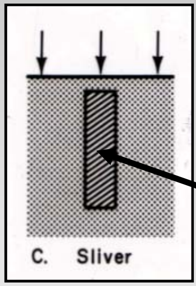


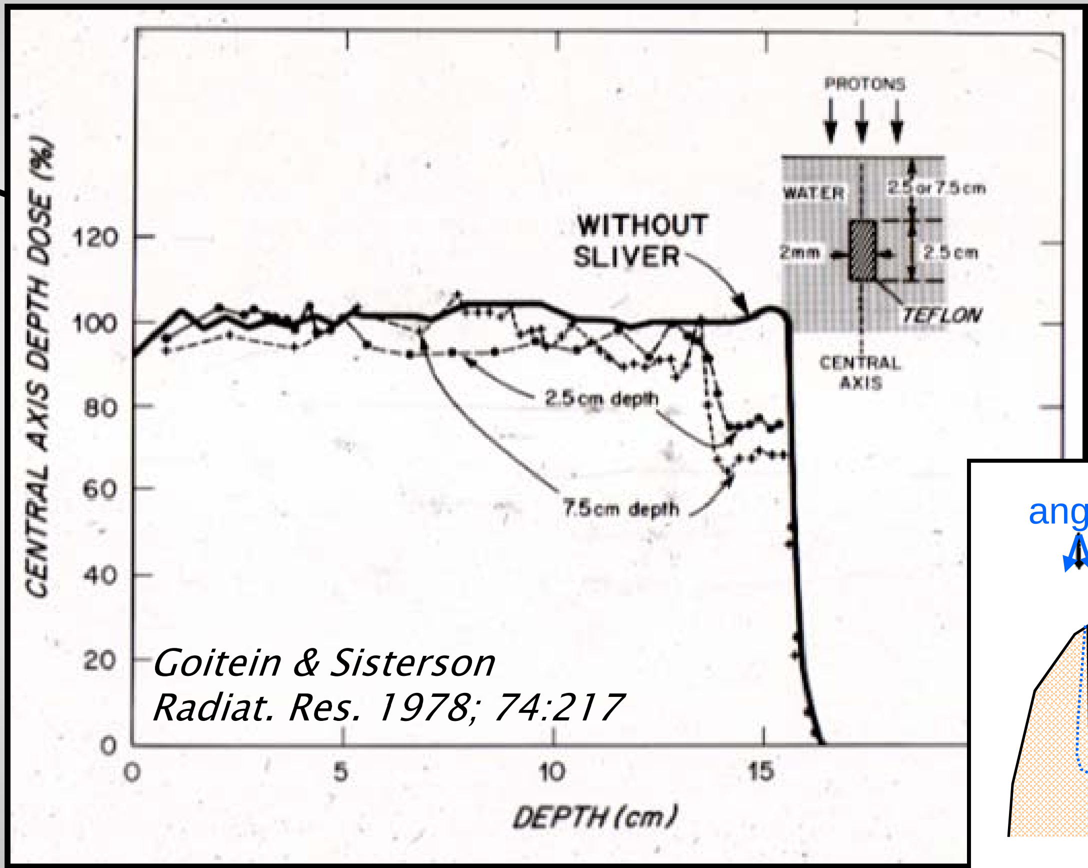
Med Phys 5:265 (1978)

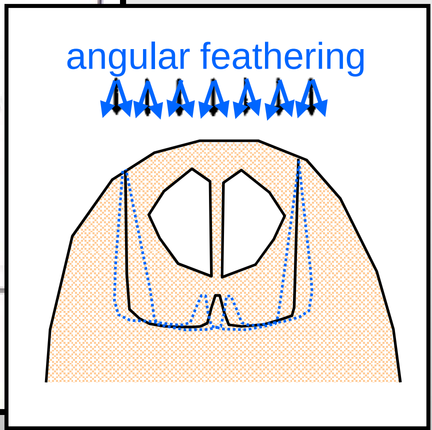
Goitein et al., Med Phys 5: 265 (1978)

Q. How wide a sliver can cause range shortening?

2mm wide Teflon "sliver"





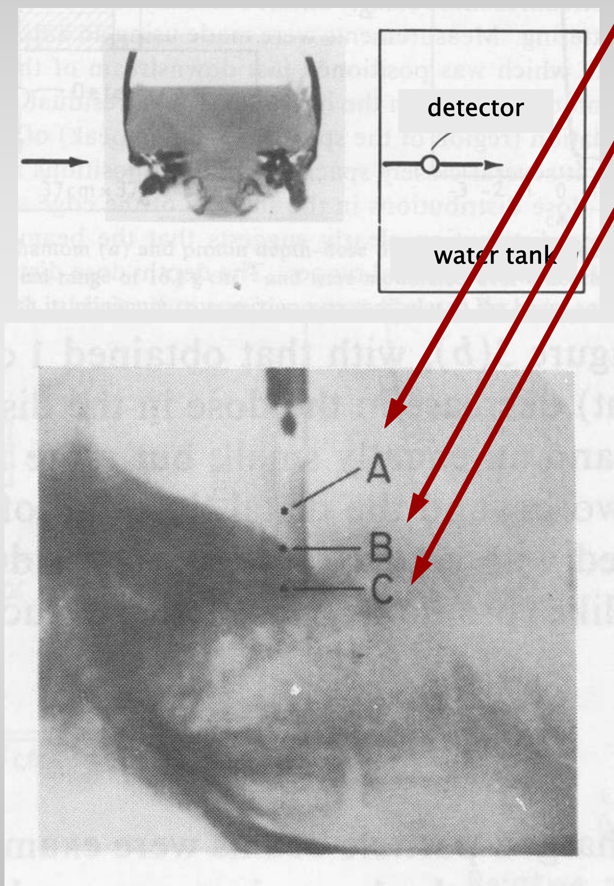


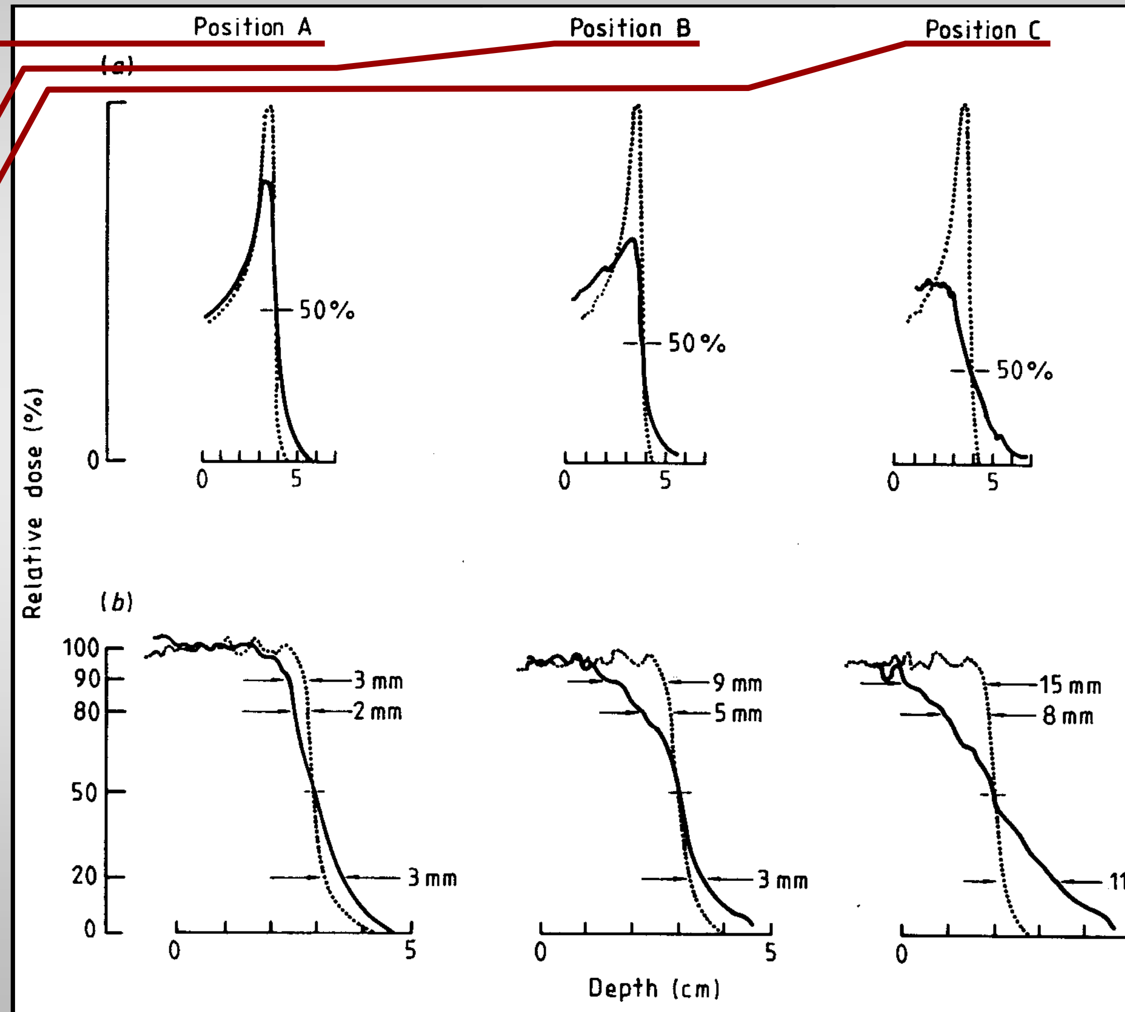
A: pretty small (~ 1mm)
– at the edge of available imaging and computation resolution!

DISTAL EDGE DEGRADATION

Human skull (water-filled)

pristine Bragg Peak

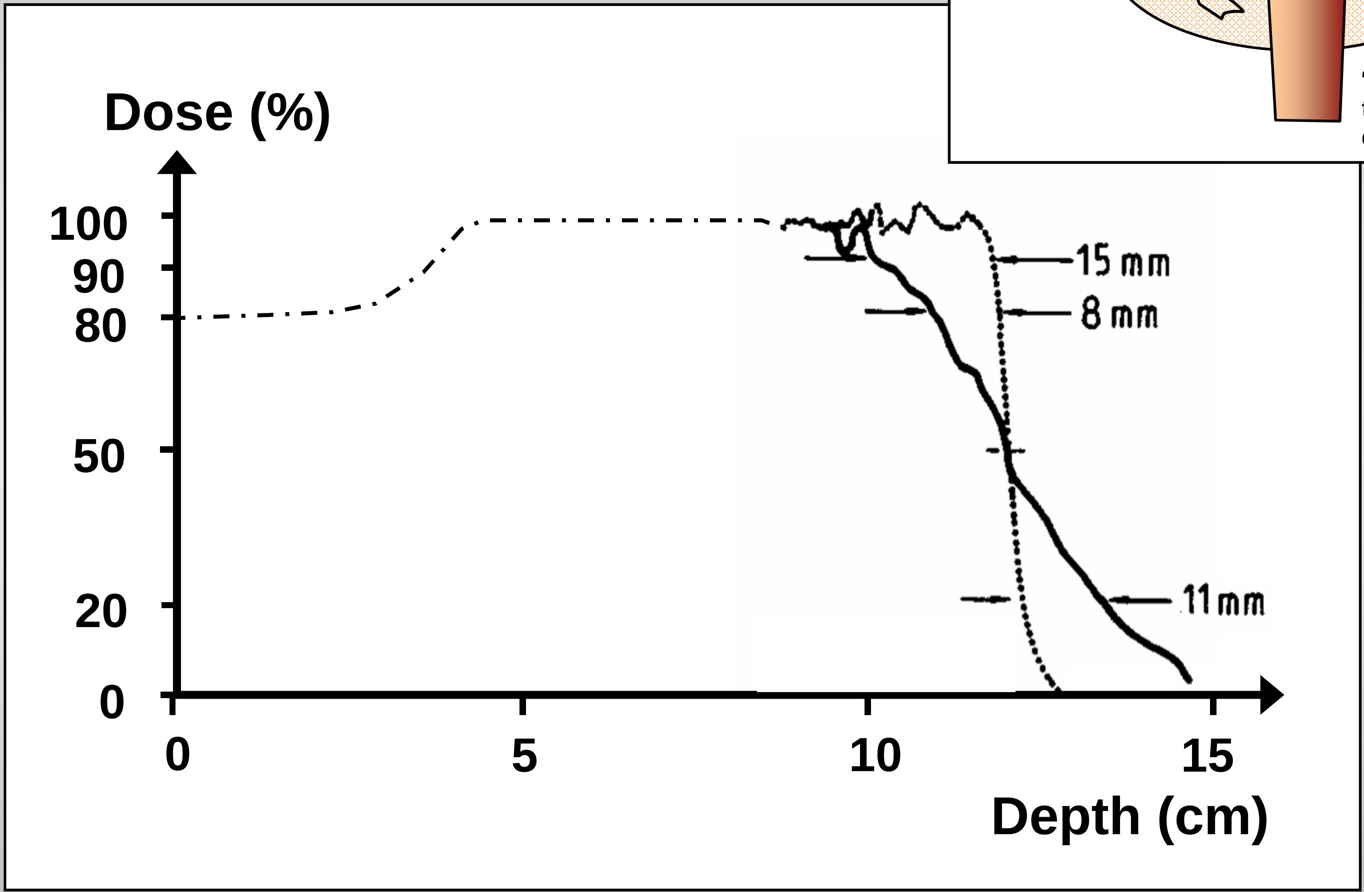


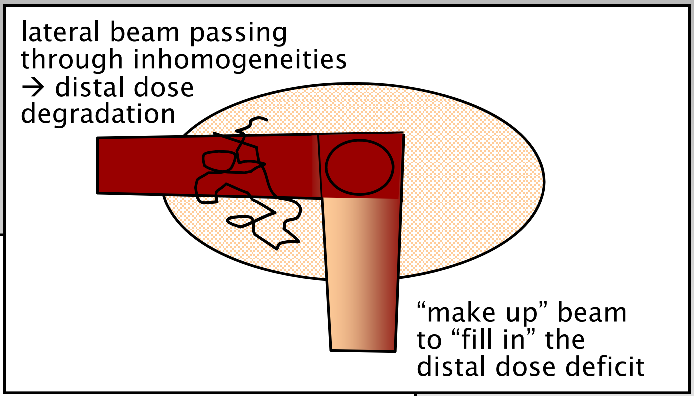


spread-out Bragg Peak

Urie et al. Phys Med Biol 1986; 31: 1

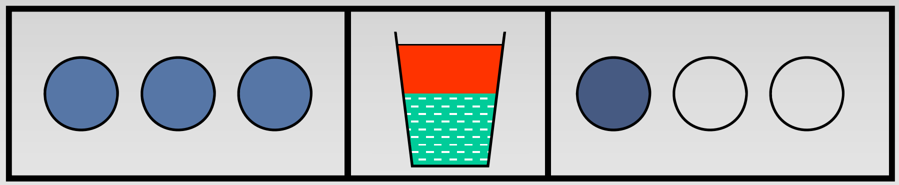
position C; SOBP



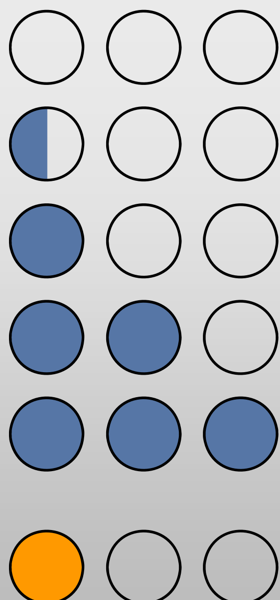


PROTON CONSUMER'S REPORT SCHEMA

past *present* *future*



done / to do



almost nothing

very little

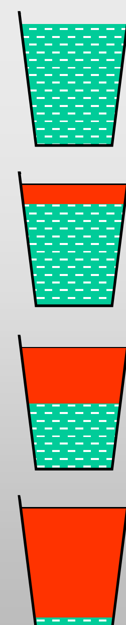
some

quite a lot

really a lot

some work to be done, but not very critical

current status



as good as it gets

mostly understood

glass half full

pretty ignorant

INTERACTION OF PROTONS – SUMMARY

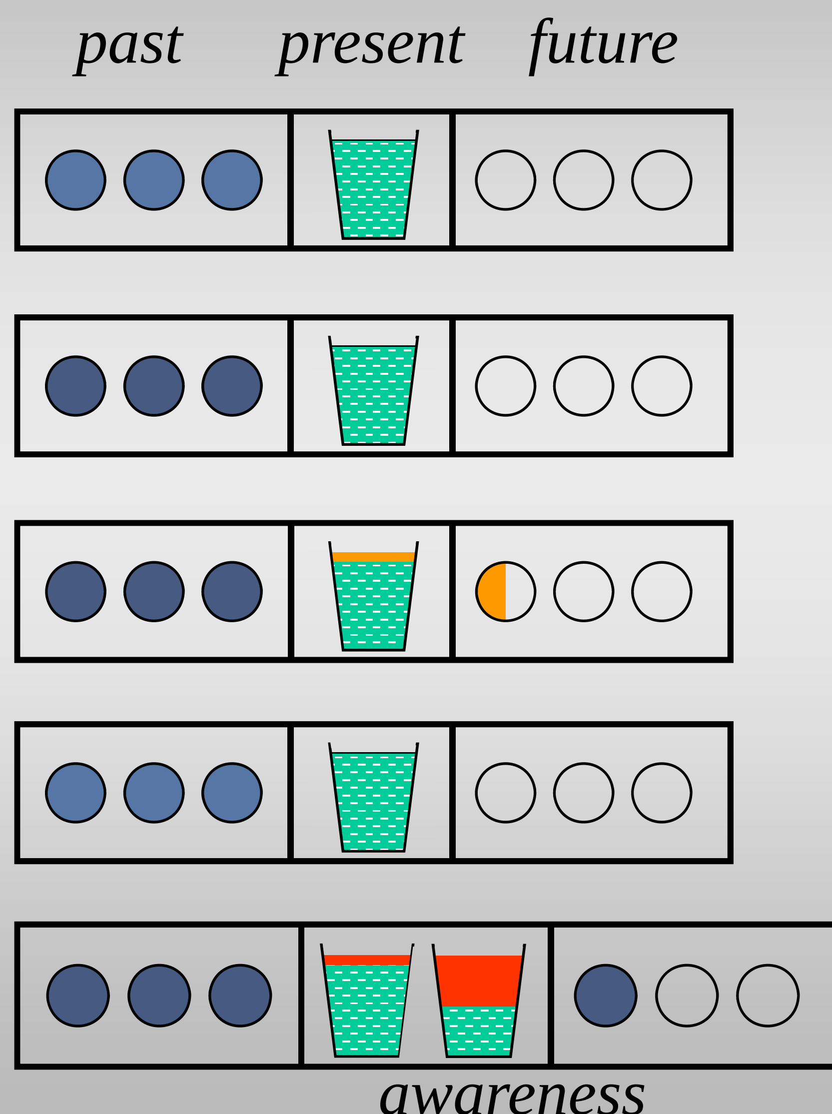
proton penetration

multiple Coulomb scattering

nuclear interactions

dosimetry

inhomogeneities



TREATMENT PLANNING

- image-based geometric design
- dosimetric design (manual)
- uncertainty
- intensity-modulated proton therapy (IMPT)
- algorithmic plan design
  - optimization and robustness

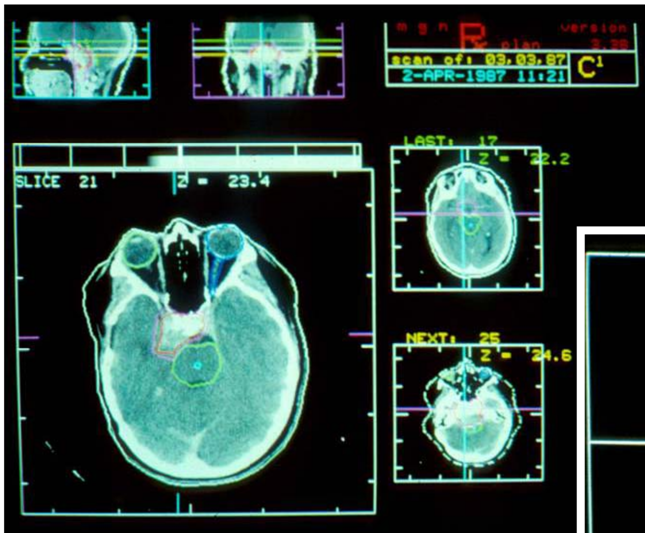
WHAT IS DIFERENT ABOUT TREATMENT PLANNING FOR PROTON THERAPY?

step		protons vs. photons
1	Evaluate the patient using all relevant diagnostic tools, and decide whether to employ radiation therapy.	~same (but protons may affect choice of modality)
2	Obtain and inter-register imaging studies with the patient lying in the position to be used for therapy.	same
3	Delineate on the planning CT the target volumes (GTV, CTV and PTV) and normal tissues.	~same (but PTV has different interpretation)
4	Establish the planning aims for the treatment.	same
5	Design one or more sets of beams, together with their weights, each of which fulfills, to the extent possible, the requirements of the planning aims.	different
6	Evaluate these plan(s) and either select one of them for use or revise the planning aims and return to step 5.	need robust optimization more vbles.
7	Finalize the prescription.	same
8	Simulate the selected plan to ensure it is deliverable.	same
9	Deliver the treatment, and verify that the delivery is correct.	~same (but QA harder)
10	Re-evaluate the patient during the course of treatment and, if necessary, return to step 5, or even 2, to re-plan the remainder of the treatment.	same
11	Document and archive the final treatment plan.	same
12	Review the treatment plan at the time of patient follow-up or possible recurrence.	same

adapted from Radiation Oncology: A physicist's-eye view. Michael Goitein. Springer, New York, 2007

see also: ICRU report 78

GEOMETRIC DESIGN – image based



use of CT

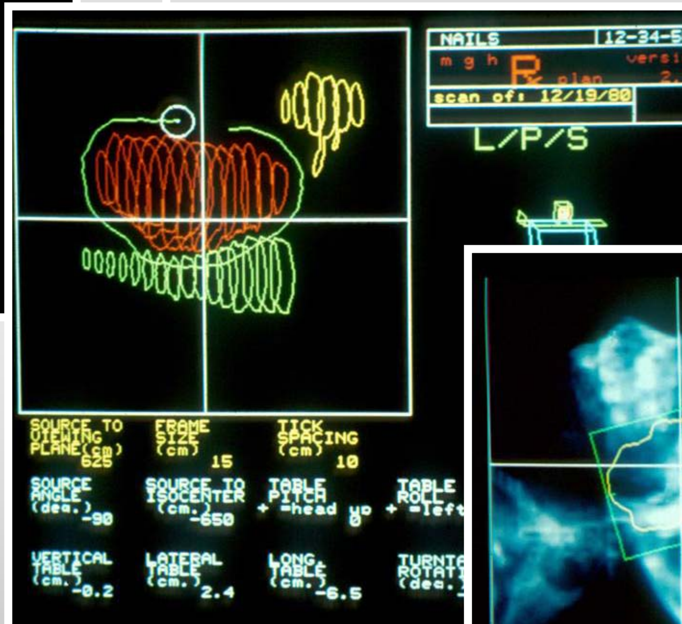
sagittal / coronal reconstructions

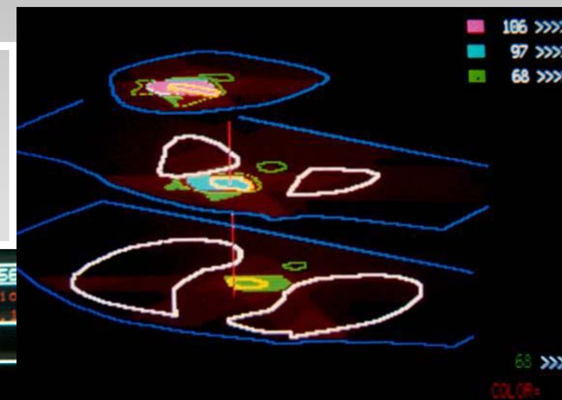
contour definition

Beam's-eye view

aperture drawing

virtual simulation





McShan et al. BJR 1979

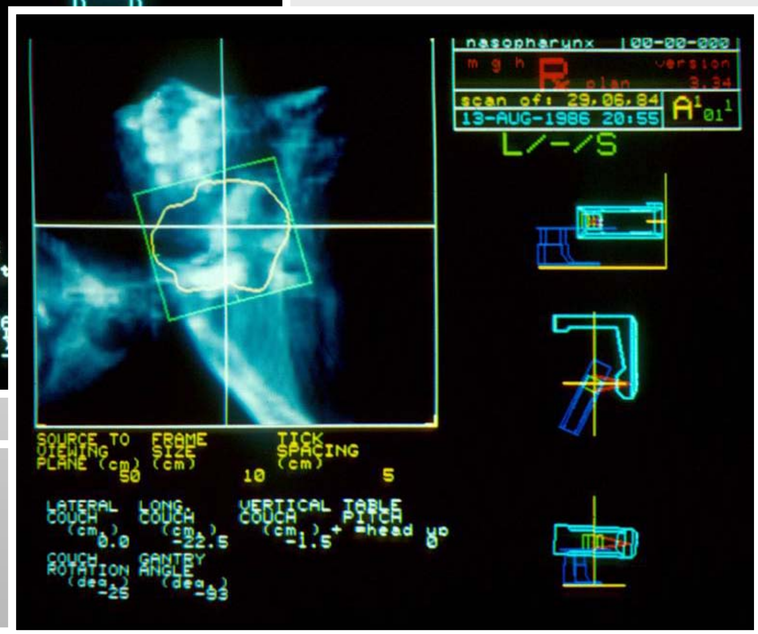


image registration (multi-modality imaging – "hat & head" technique Chen, Kessler, Pelizzari…)

DRRs

reference for setup film

DOSIMETRIC DESIGN

- algorithms

  broad beam – radiological path length

  pencil beam *e.g. Hong et al. A pencil beam algorithm for proton dose calculation. Phys Med Biol 41:1305–1330*

  Monte Carlo

  e.g. GEANT,
  purpose-written code

- dose display

  color wash (with scale!)

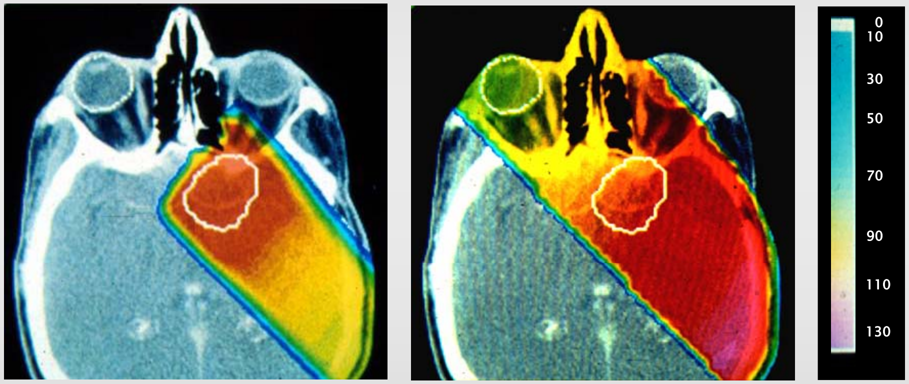
  side-by-side display

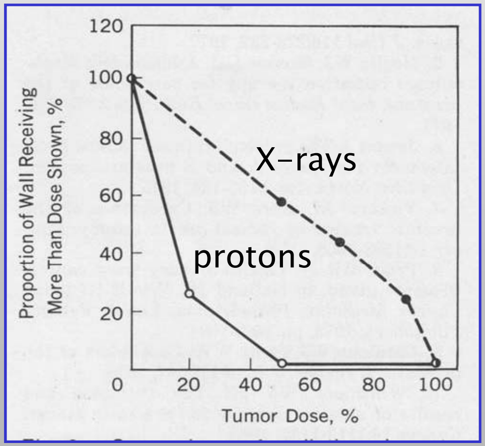
  dose-difference displays

- plan assessment and comparison

  DVHs

  score functions





Shipley et al. Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 1979; 241:1912

UNCERTAINTY

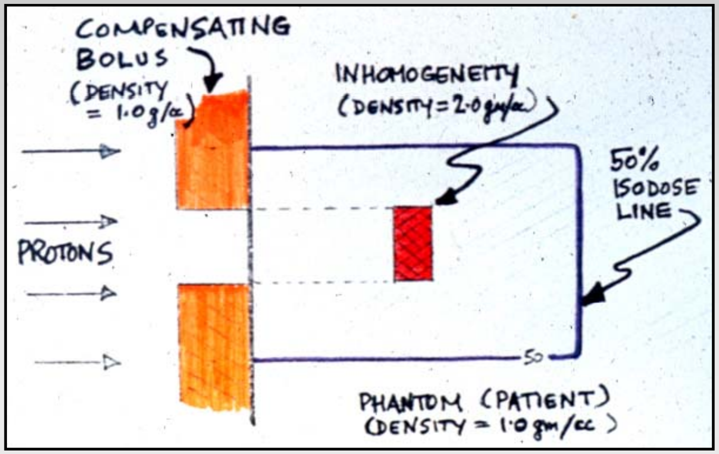
- Virtually all aspects of treatment planning are subject to significant (mainly systematic) uncertainties, such as:
  - definition of gross tumor, CTV, and normal anatomy
  - patient and organ localization and movement
  - dose estimation
  - treatment delivery
  - etc. etc.

(Goitein. Calculation of the uncertainty in the dose delivered in radiation therapy. Med Phys. 1985; 12:608-612)

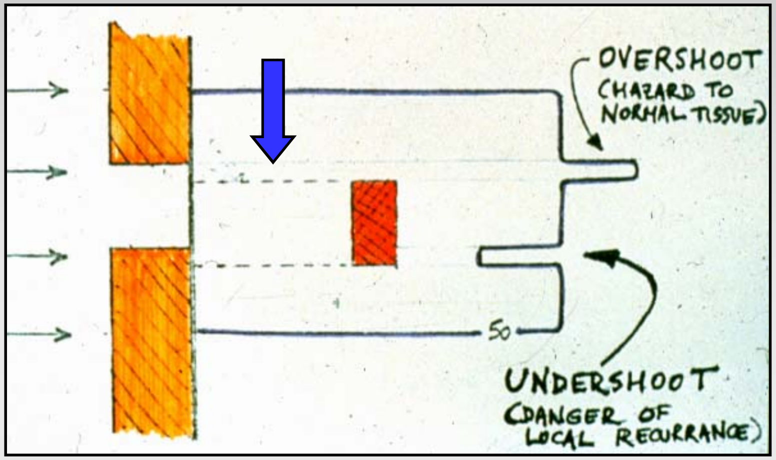
- It is the job of the plan designer(s) to:
  - assess the uncertainties (at a given level of confidence)
  - take steps to minimize them to the extent practically possible
  - plan the treatment taking the residual uncertainties into account

COMPENSATION FOR MIS-REGISTRATION

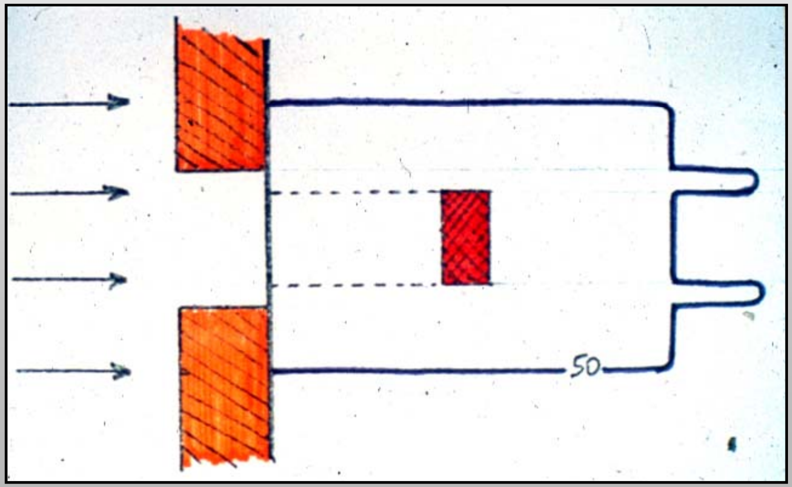
idealized compensation

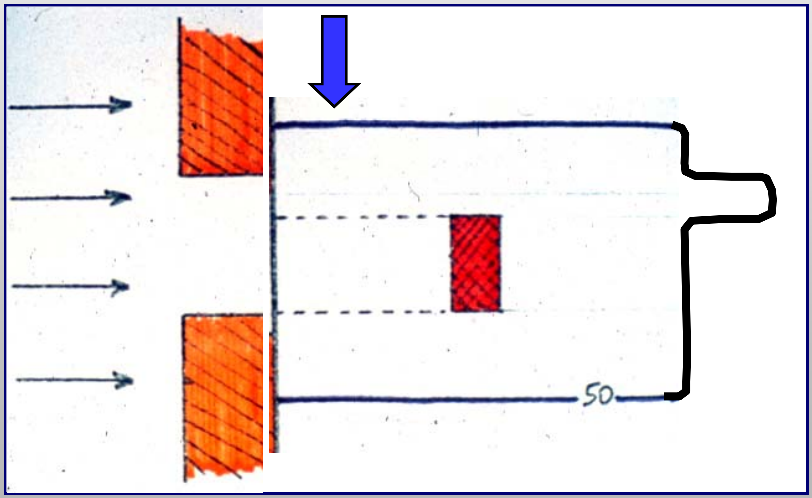


but, mis-registration can lead to undershoot:



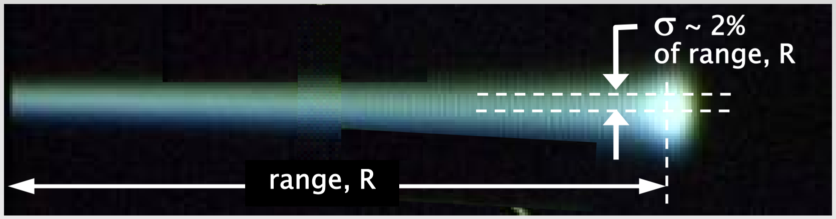
solution, (if one gives priority to tumor coverage):
"open up" the compensator (at the price of certain overshoot)



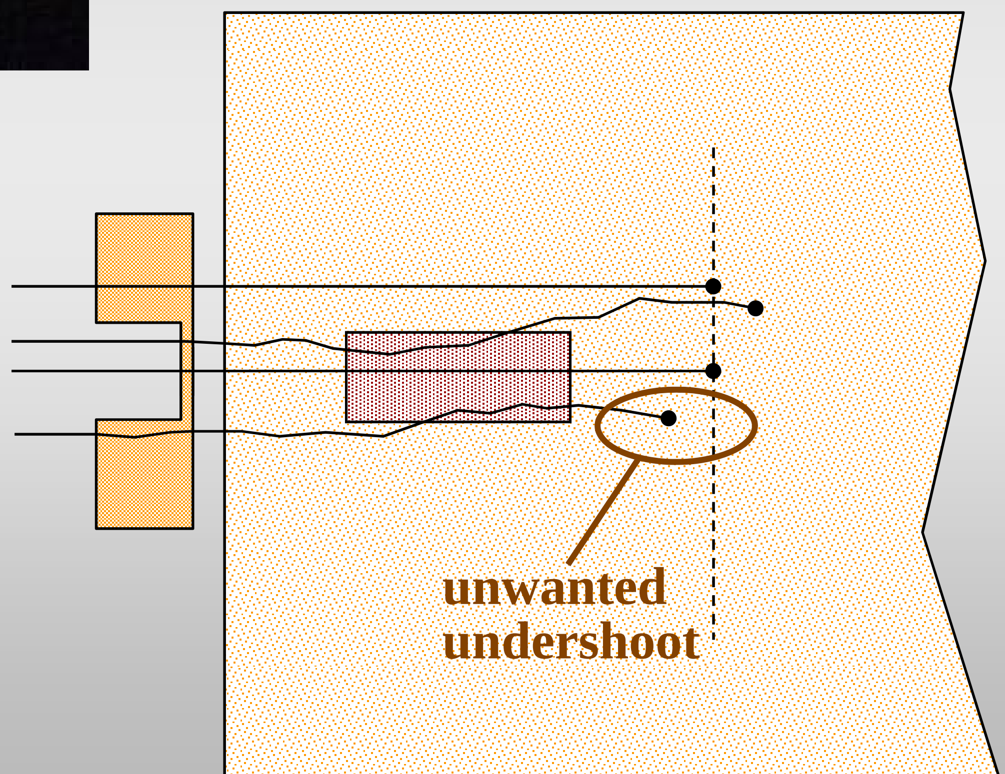


COMPENSATION FOR MULTIPLE SCATTERING

At 15cm depth, $\sigma \simeq 3$mm



Based on a figure courtesy of Eros Pedroni, PSI



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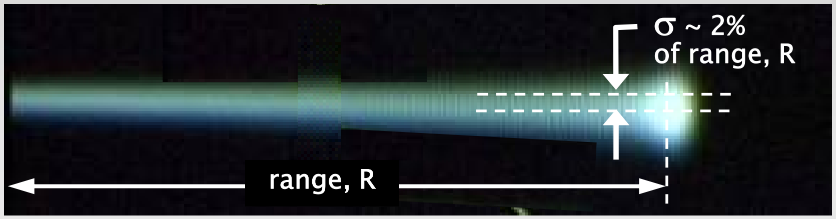
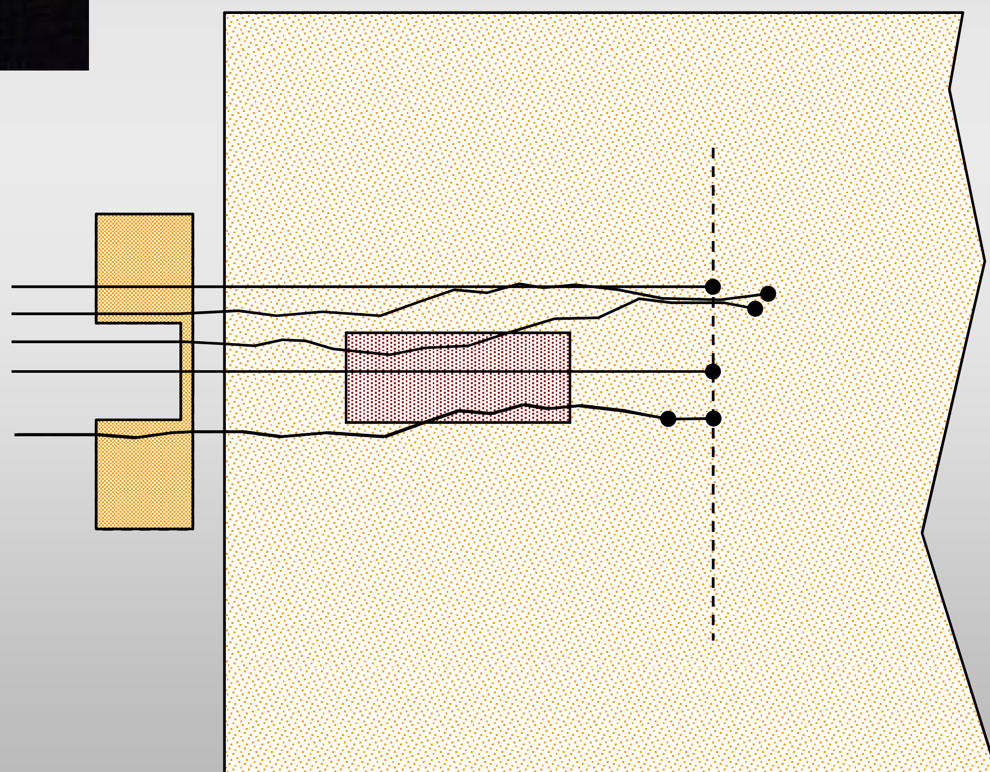
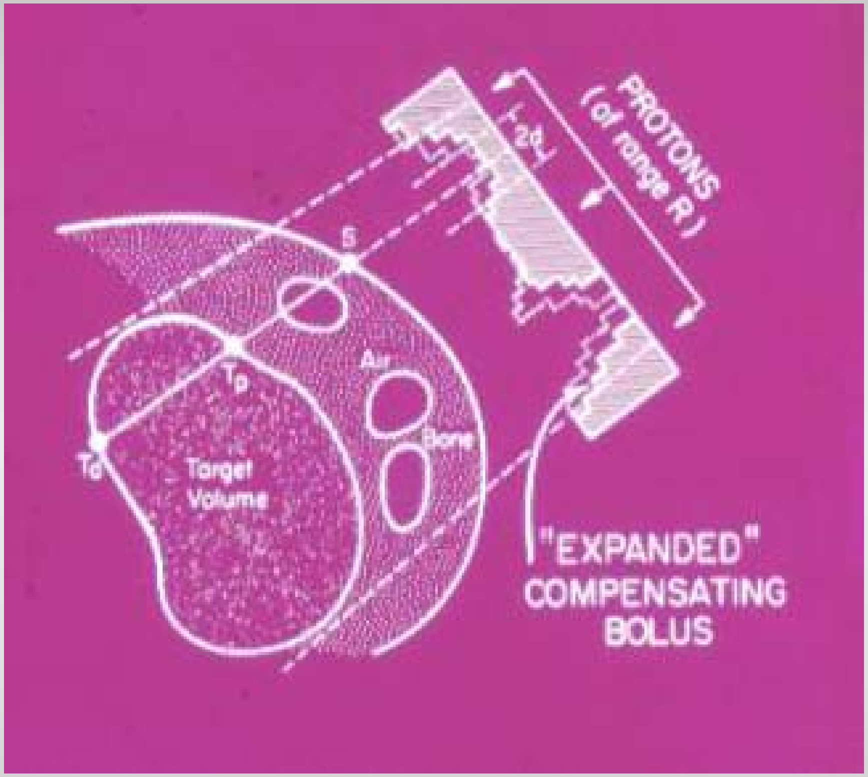


Based on a figure courtesy of Eros Pedroni, PSI

so, expand compensator



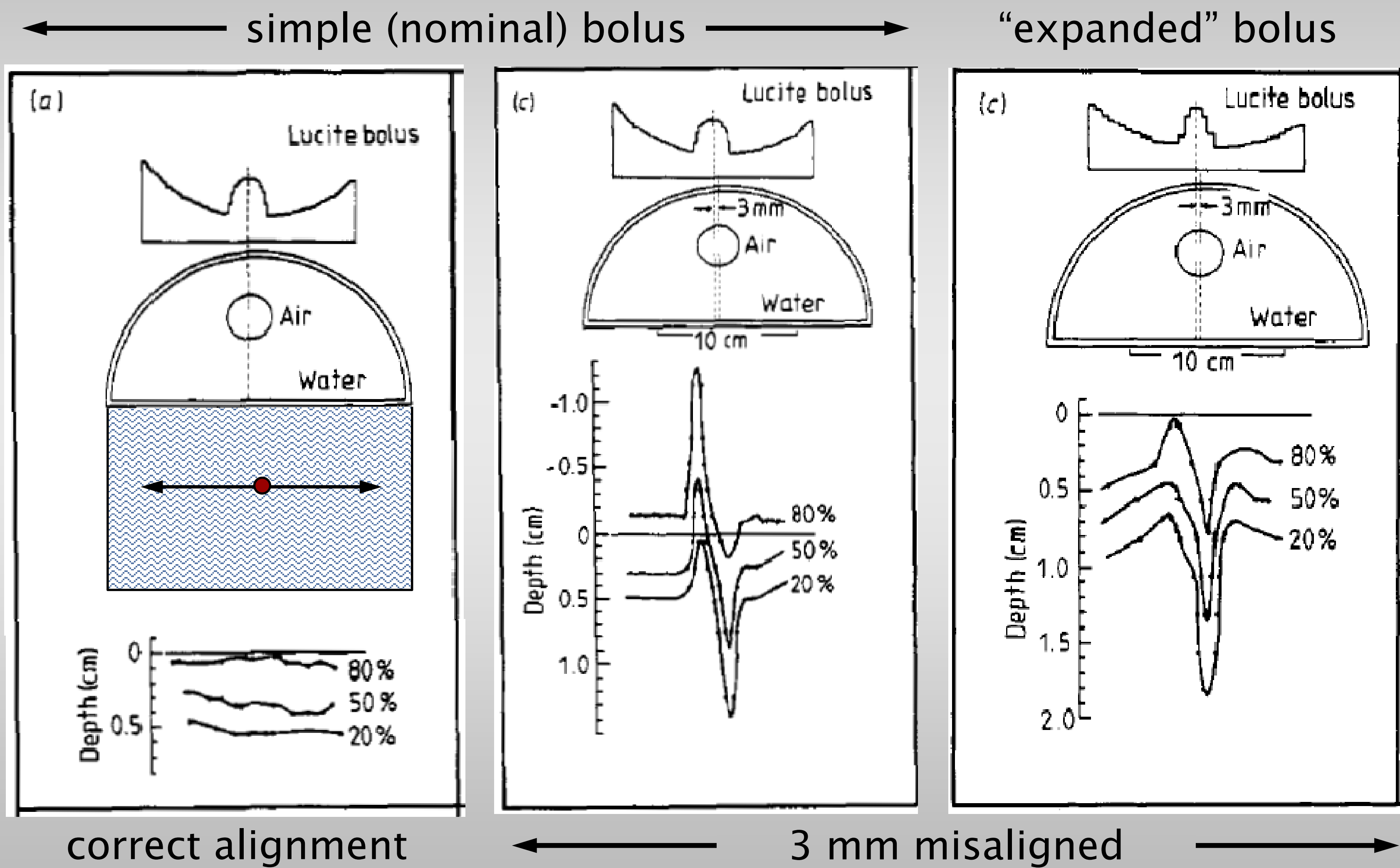
COMPENSATOR DESIGN (physical and virtual)



compensates for mis-registration
and multiple scattering

Urie M et al. (1984) Compensating for heterogeneities in proton radiation therapy. Phys Med Biol 29:553–566

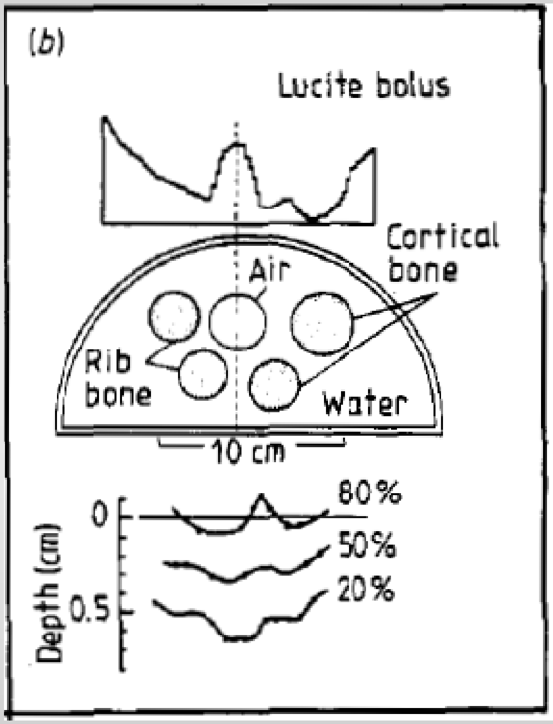
COMPENSATING FOR REGISTRATION ERROR – simple inhomogeneity

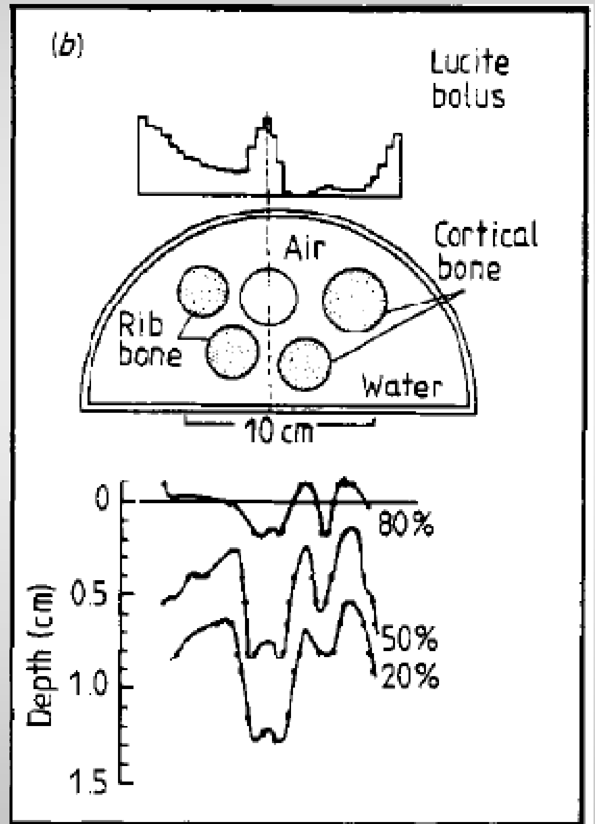


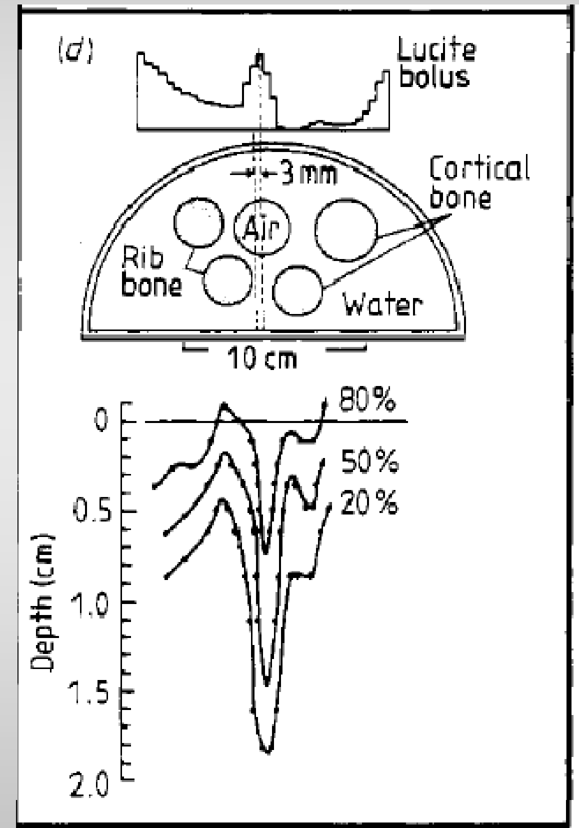
Urie M et al. (1984) Compensating for heterogeneities in proton radiation therapy. Phys Med Biol 29:553–566

COMPENSATING FOR REGISTRATION ERROR
– complex inhomogeneities

simple (nominal) bolus ← "expanded" (by 3mm) bolus →





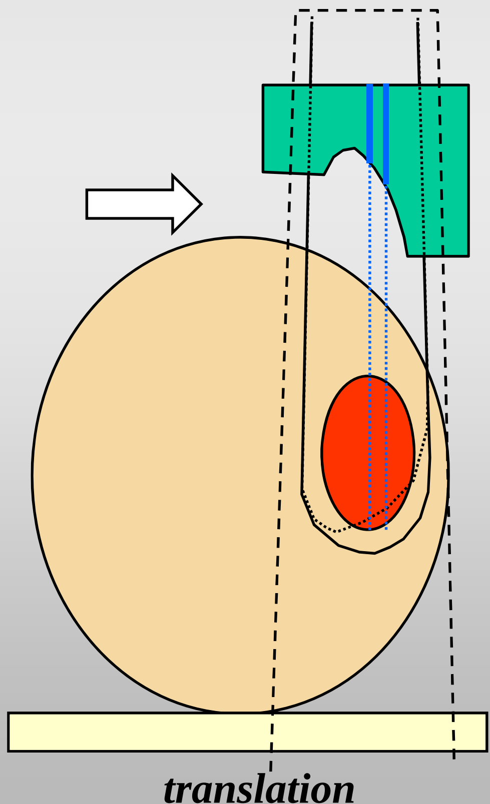


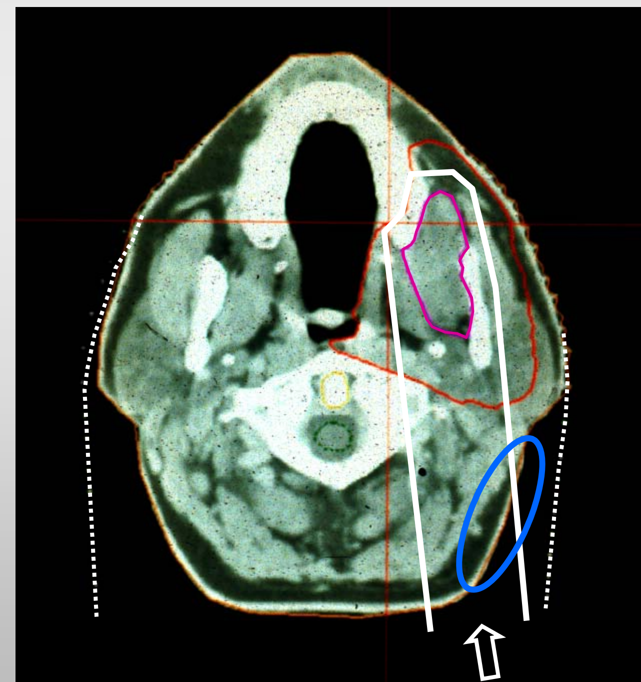
← correct alignment → 3 mm misaligned

Urie M et al. (1984) Compensating for heterogeneities in proton radiation therapy. Phys Med Biol 29:553–566

BEAM DIRECTION NEAR-TANGENT TO A SKIN:TISSUE INTERFACE

- The greatest inhomogeneity is that which exists at the interface between the patient and the surrounding air
- if the beam direction is near-tangent to a skin:tissue interface, the dose distribution can be very sensitive to patient motion or misalignment

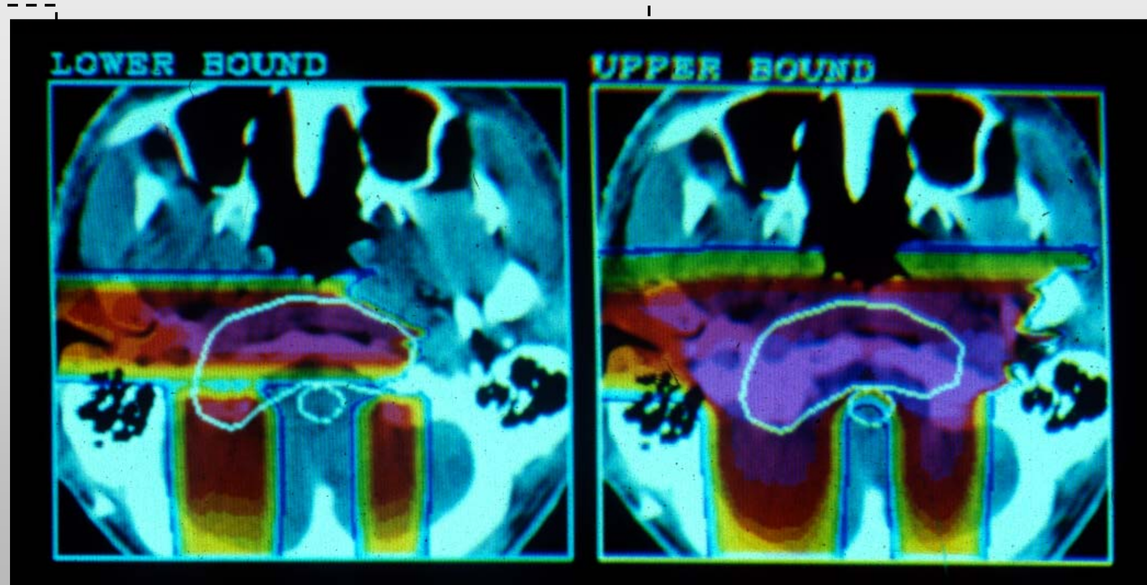




CALCULATION & DISPLAY OF UNCERTAINTY

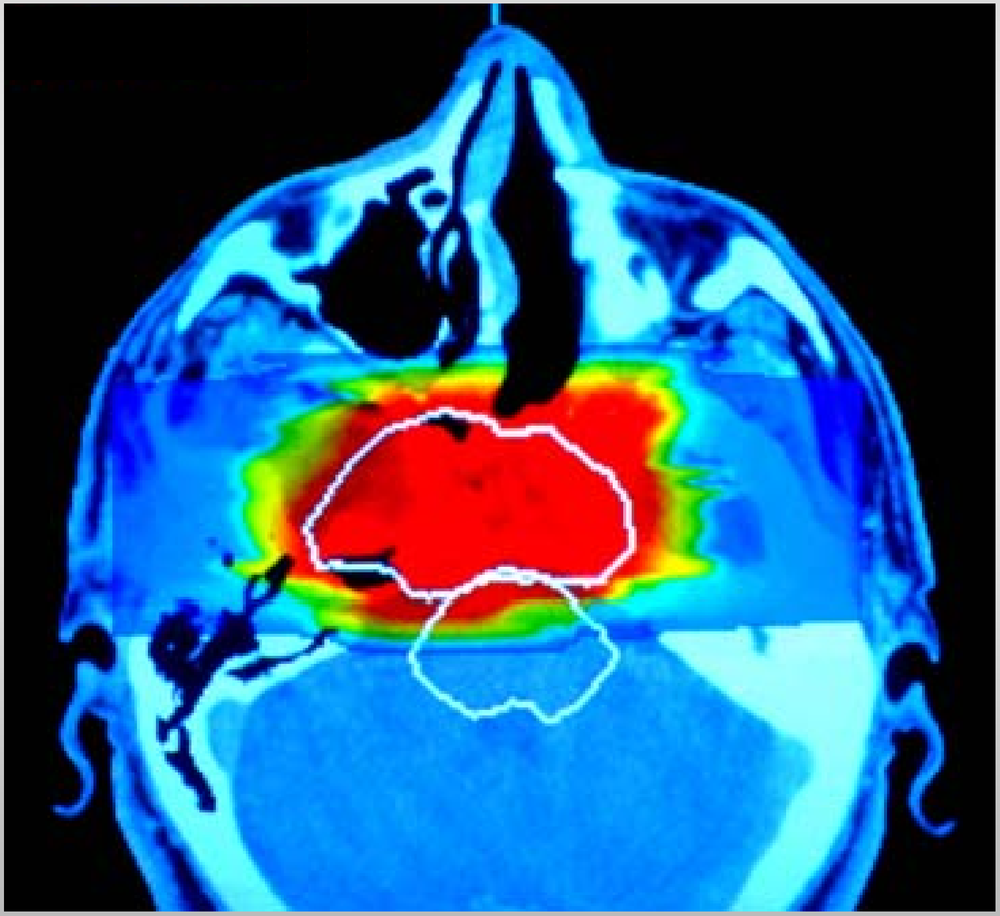
- Compute 3 dose distributions

  - **nominal** — dose at a pixel computed using nominal values of all variables
  - **lower bound** — dose at a pixel computed using the value of each variable that would tend to yield the lowest dose
    (but use the computed “upper bound” value, if lower)
  - **upper bound** — dose at a pixel computed using the value of each variable that would tend to yield the highest dose
    (but use the computed “lower bound” value, if higher)



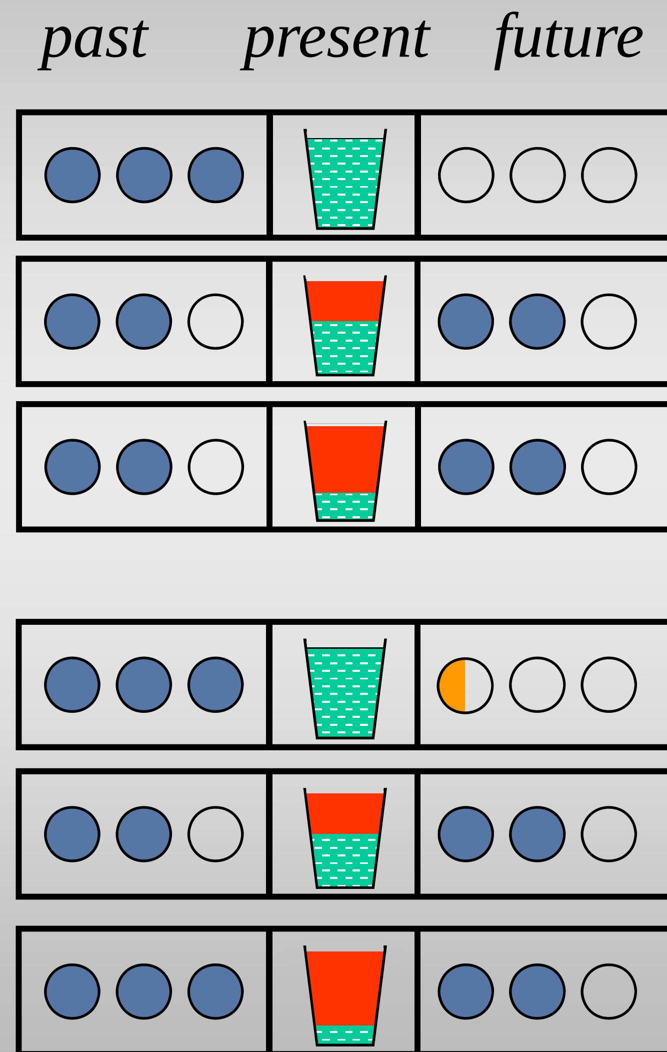
A MAJOR CONSEQUENCE OF UNCERTAINTY

- larger-than-desired safety margins



GEOMETRIC DESIGN, DOSE CALCULATION & UNCERTAINTY

- image-based geometric design
  - use of imaging
  - image registration
  - time variations (4D)
- dosimetric design (manual)
  - broad- & pencil-beams
  - Monte Carlo
- uncertainty
  - computation, and allowance for the uncertainties



TREATMENT PLANNING

- image-based geometric design
- dosimetric design (manual)
- uncertainty
- intensity-modulated proton therapy (IMPT)
- algorithmic plan design
  - optimization and robustness

OPTIMIZATION

- Why is the subject of optimization important?
  1. In IMPT, which presently requires pencil-beam scanning, there are <u>so many variables</u> that one needs a computer algorithm to set them

     perhaps 10,000 pencil beams or more, times the 3 variables of intensity, depth of penetration and transverse size for each pencil beam
  2. Even in uniform-beam irradiation, the choice of penetration (which can vary over the field, is difficult and can benefit from computer-based solutions (e.g. field-patching)
- Optimization requires a search algorithm to find the optimal set of variables, and a score function. Generally:

  a solution to the search problem is not hard to find, though it may be computationally demanding

  a clinically meaningful score function is extremely difficult to find
- In proton therapy, however

  due to the almost two orders of magnitude more variables, the search problem becomes even more demanding

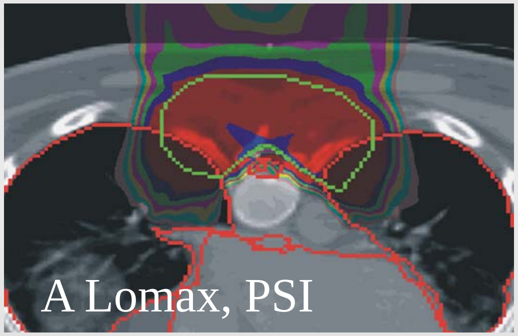
  the score function is further complicated due to uncertainties in the penetration of each pencil beam

ROBUST OPTIMIZATION

- One simply has to deal with uncertainties.
- A robust plan is one which is not too negatively affected by the unavoidable or irreducible uncertainties.
- There are two ways of achieving robustness:
  - find the plan which has the least-bad "worst case"

    the worst case is the (unphysical) dose distribution for which, for a given level of uncertainty in the treatment variables

    in each voxel within the PTV the dose is set to the lowest possible dose; and
    in each voxel within an OAR the dose is set to the highest possible dose.



see, also: Shalev *et al*. Treatment planning using images of regret. Med Dosim. 1988;13(2):57-61.

  - find the plan which on average has the best score – when averaging over all sources of uncertainty

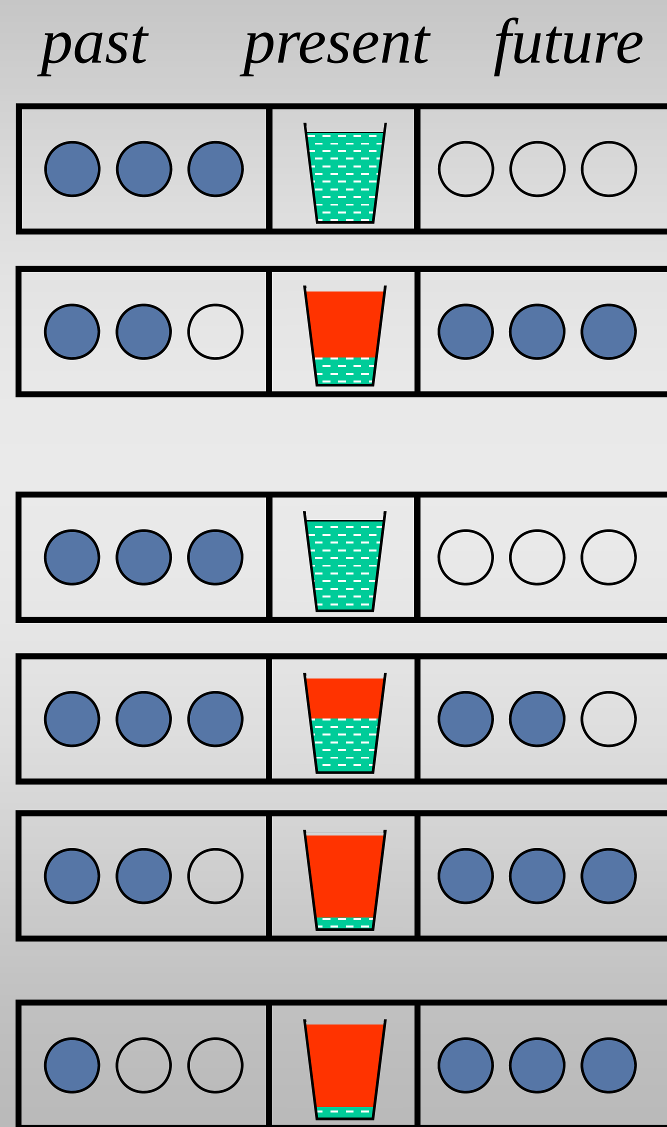
Unkelbach J and Oelfke U Phys. Med. Biol. 49 (2004) 4005–29

Unkelbach et al. Accounting for range uncertainties... Phys. Med. Biol. 52 (2007) 2755–2773

these approaches have demonstrated very promising results

IMPT, OPTIMIZATION AND ROBUSTNESS

- IMPT
  - understanding of the problem
  - development of solutions
- OPTIMIZATION
  - search techniques
  - dose-based optimization
  - biological optimization
- ROBUST PLANNING



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4. Clinical Application
    - clinical experience
    - clinical trials

GENERAL STATUS OF THE TECHNOLGY OF PROTON THERAPY

- There is a misapprehension that, since proton therapy has been developed over about half a century, the technology is mature.
- It is not.
- This is largely because:

  the early experience was in research environments in which less-than-efficient procedures were tolerated

  the current commercial offerings largely copied the existing technologies (with the addition of gantries)

  IMPT is a very recently-recognized possibility and has not had time to be satisfactorily commercially developed

- But, don't be too alarmed, because:

  proton therapy is currently being delivered with the existing technology to the benefit of large numbers of patients

  the developments are needed to allow protons to reach their full potential, and to be used in a clinically streamlined fashion.

BEAM GENERATION

- The technology of currently-used proton accelerators is pretty well developed

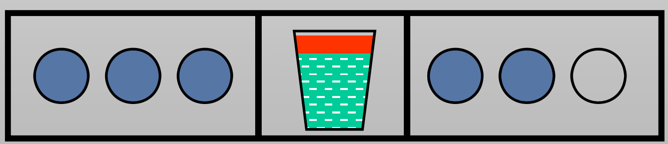
  synchrotrons
  cyclotrons

  both are adequate and reasonably reliable – except that:

- There is still an intensity problem – reflected in:

  low beam intensity at low energies (cyclotrons)
  too large pencil beam sizes (caused also by other factors)

- Cost remains a factor (we're still waiting for true marketplace competition 15 years after MGH signed the first commercial contract for a proton facility)



NEW TECHNOLOGIES FOR PROTON GENERATION

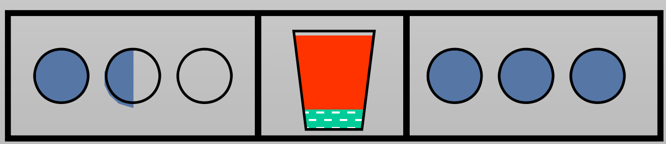
- Good luck

- but, beware!

  remember the fate of d-T generators in neutron therapy

- and, don't compromise performance – e.g.

  lowering the maximum energy
  failure to support IMPT
  etc.



BEAM SHAPING: SCATTERED BEAMS

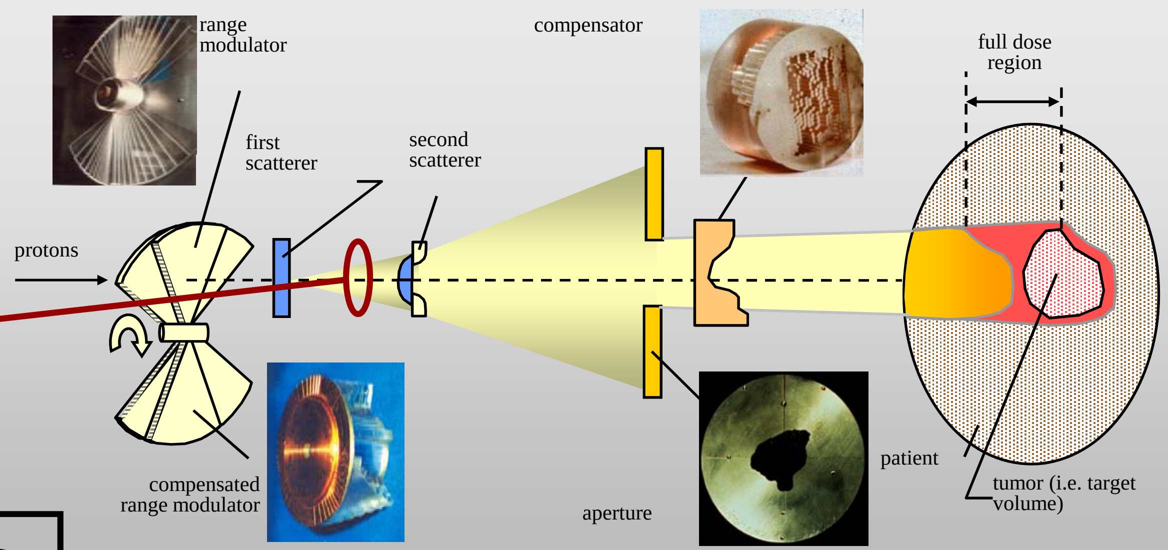
- The technology has been very fully developed
  - primarily by Andy Koehler, Bernie Gottschalk, and colleagues at the Harvard Cyclotron Laboratory
- Current commercial systems primarily use the "historic" technology, including double-scattering – with a few enhancements, e.g.
  - automatically selectable range modulator wheels
  - beam gating to vary the depth of the SOBP
- The depth characteristics are fairly satisfactory, using the current range modulator technology
  - except for low energies for which the Bragg peaks are too narrow to stack easily and a better method of spreading them (e.g. ridge filters) is needed

BEAM SHAPING: SCATTERED BEAM PENUMBRA

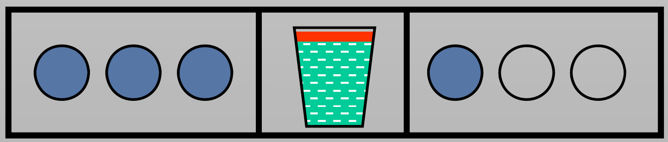
- But, beam penumbra in the current scattered beam implementations is very inadequate (worse than Cobalt-60 in many cases)
- For scattered beams, the historically achieved penumbrae were OK due to their long throw, but in the current gantry implementations the penumbra is far from satisfactory.

This is because they use double-scattering with a relatively short throw (SAD)

large effective source size (a few cm)

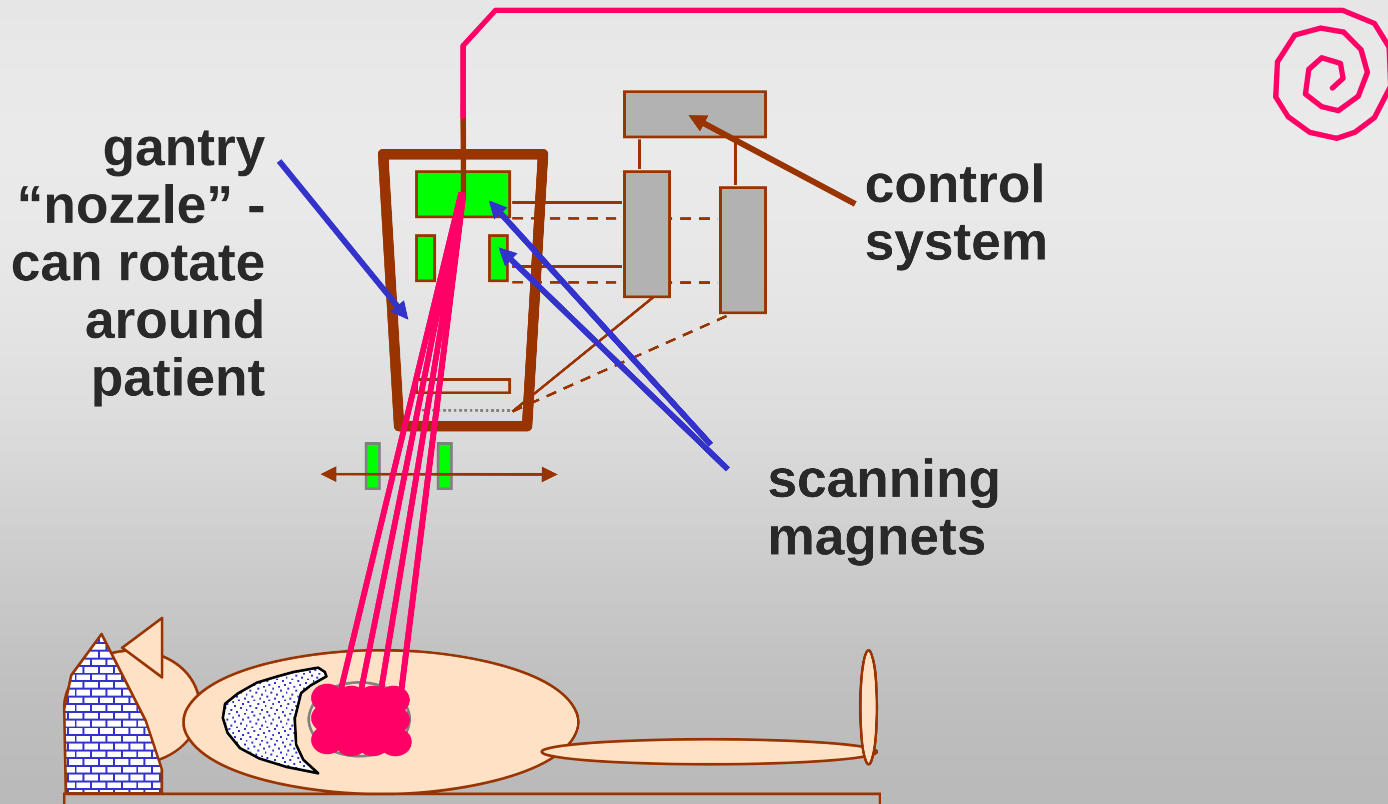


scattered beam technology



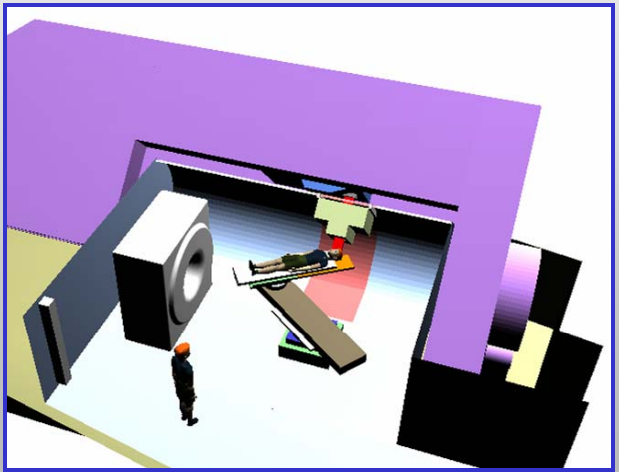
BEAM SHAPING: SCANNED BEAMS
and intensity-modulated proton therapy (IMPT)

- IMPT requires the use of a pencil beam of protons whose Bragg peak is scanned throughout the target volume while its energy (penetration) and intensity are varied at will.

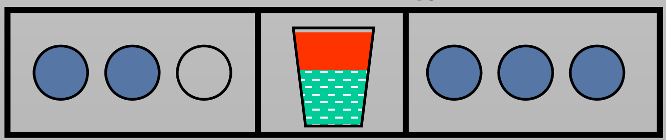


BEAM SHAPING: SCANNED BEAMS
and intensity-modulated proton therapy (IMPT)

- IMPT requires the use of a pencil beam of protons whose Bragg peak is scanned throughout the target volume while its energy (penetration) and intensity are varied.
- The only significant experience with IMPT to date has been at the Paul Scherrer Institute (PSI) in Switzerland where they developed, and have used since 1996, a prototype so-called spot-scanning gantry
- PSI are now building a second gantry featuring isocentric rotation and faster scanning (due to start treating in 2010)
- Commercial scanning systems are just now in their infancy.



IMPT technology

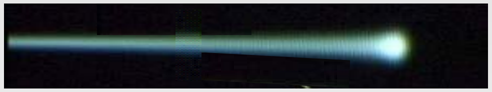


BEAM SHAPING: SCANNED BEAM PENUMBRA

- In scanned beams, the beam penumbra is set by the diameter of the pencil beam near the end of range.
- This has two components:

  scattering in the patient

  about which technology can do nothing

  pencil beam size in the absence of the patient

  which is entirely due to the technology

- If one wants to at least match, at a depth of 10cm, typical linac penumbrae of about 7mm (80-20%), the pencil beam size at isocenter in the absence of the patient (i.e. due to the technology) needs to be no more than about:

  $\sigma \approx$ 3.5 mm – i.e. a fwhm of no more than $\approx$ 8 mm

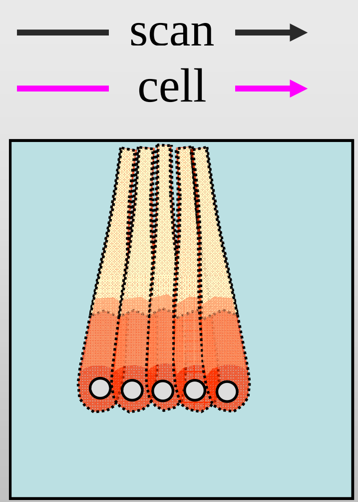
- Current implementations fall short of this important goal.

INTERPLAY EFFECT

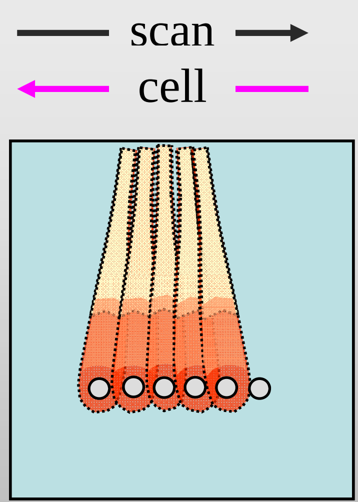
- The main downside of beam scanning is that, if there is motion of the patient and/or the tumor, so-called interplay effects can lead to up-and-down dose variations within the target (dose mottle).

Phillips M et al. Effects of respiratory motion on dose uniformity with a charged particle scanning method. Phys Med Biol. 1992 Jan;37(1):223-34

Bortfeld T et al. Effects of intra–fraction motion on IMRT dose delivery… Phys Med Biol 47:2203–2220.



cell has received
~5 times intended dose



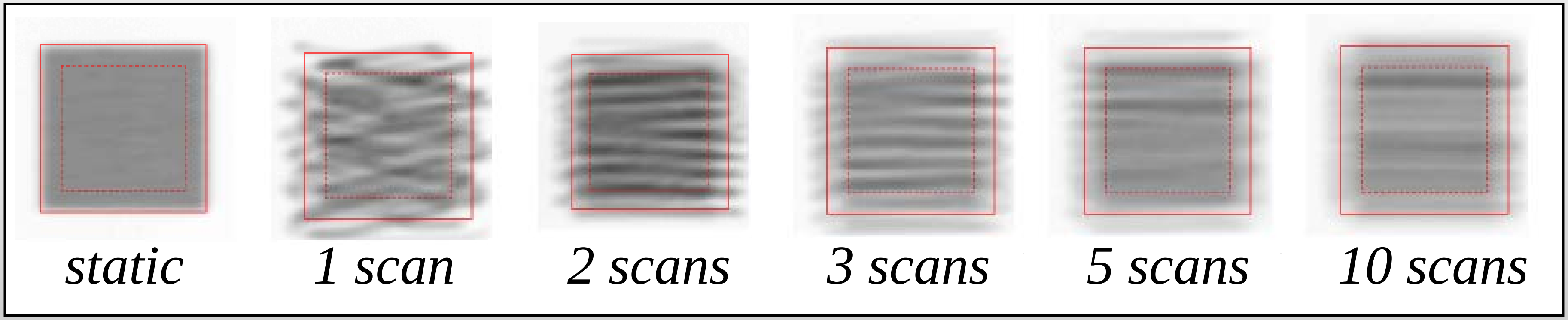
cell has received
~0 times intended dose

Dose mottle is not just theoretical. It has been observed at about the 14% (SD) level in an animal experiment at PSI, caused merely by ~2mm movements of the mouse intestine irradiated in a scanned 10 mm pencil beam!

Gueulette et al. IJROBP 2005;62:838-845

CURRENT SOLUTION(S) TO THE INTERPLAY PROBLEM

- First, reduce the amount of motion to the extent possible
  - respiratory gating
  - abdominal compression
  - tumor tracking
- Then, **repaint** the field <u>many</u> times. But…



Grözinger et al. Simulations to design an online motion compensation system for scanned particle beams Phys. Med. Biol. 51 (2006) 3517–3531

and thesis: http://elib.tu-darmstadt.de/diss/000407/

BEAM SHAPING

- In depth

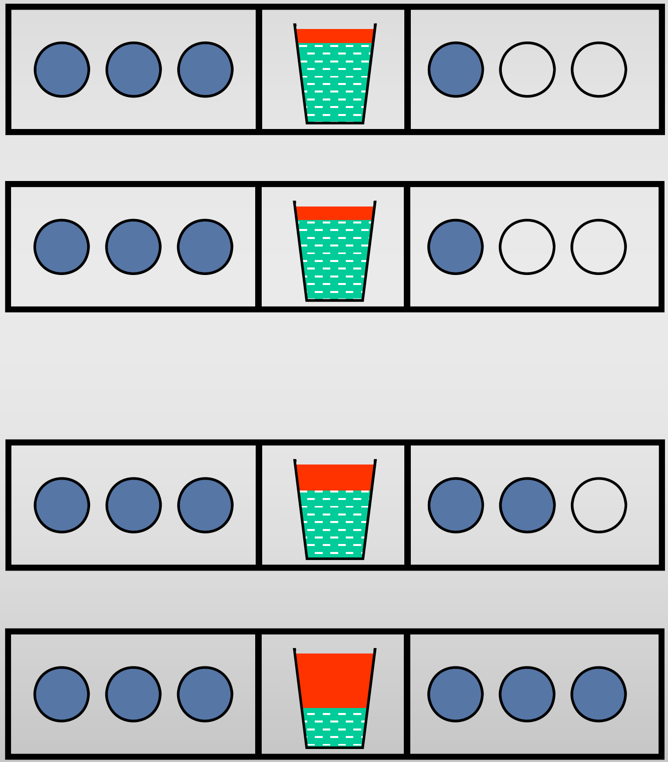
    scattered beams

    scanned beams

- Laterally (penumbra)

    scattered beams

    scanned beams



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IMMOBILIZATION AND MOTION MANAGEMENT

- Proton therapy has, from its very beginning, emphasized accuracy of beam placement (relative to the target volume) and tight margins where possible and indicated.
- This is for two reasons:

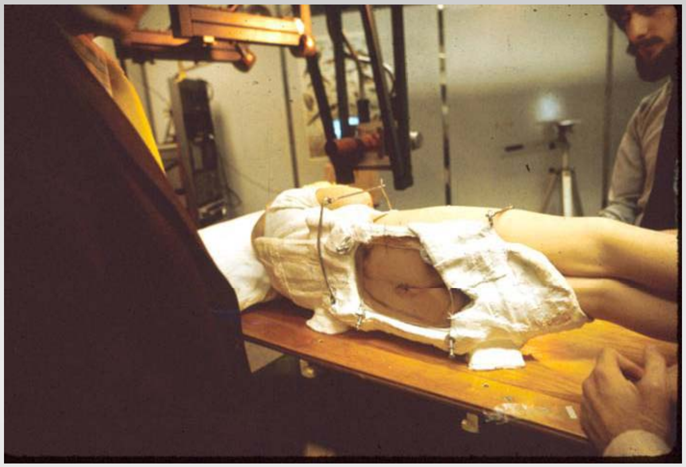
  compensators need to be in accurate registration with the inhomogeneities and beam shapes they are intended to compensate for in order to avoid an unintended distribution of dose

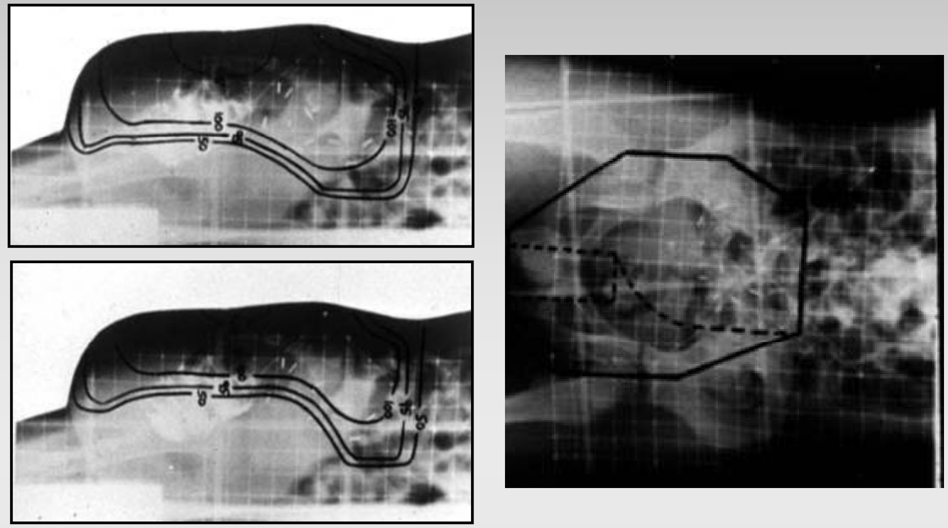
  a main goal of proton therapy is to minimize the volume of normal tissue outside the target volume which receives a high dose

- This has resulted in a number of developments which have found wide application

PLANNING, IMMOBILIZATION AND LOCALIZATION

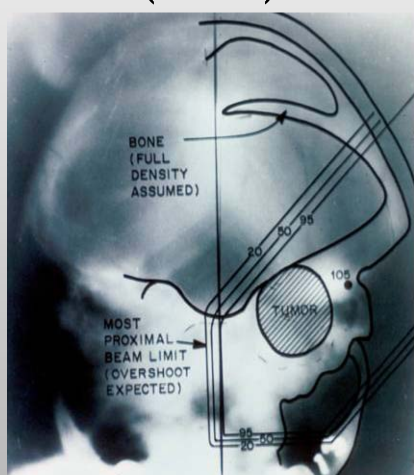
patient #1 at HCL (1974)





planning based on radiographs

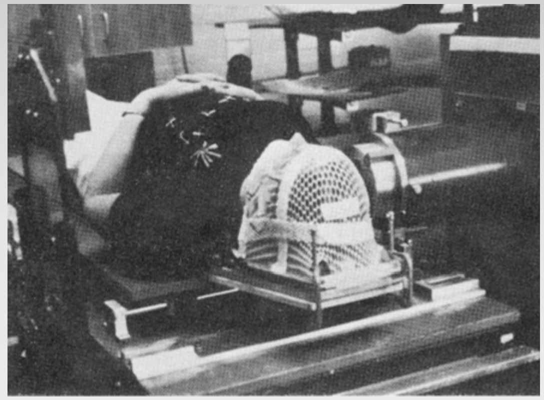
patient #2 at HCL (1974)

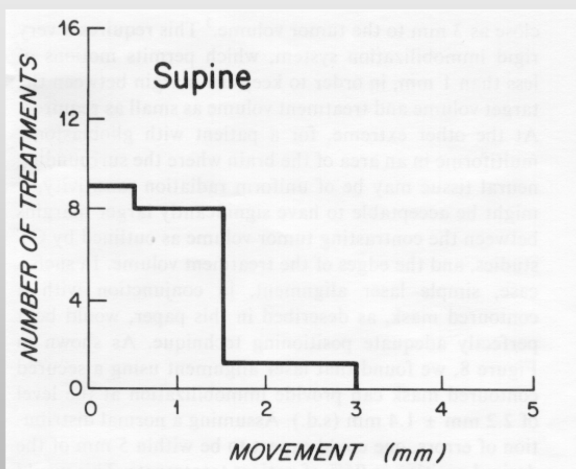


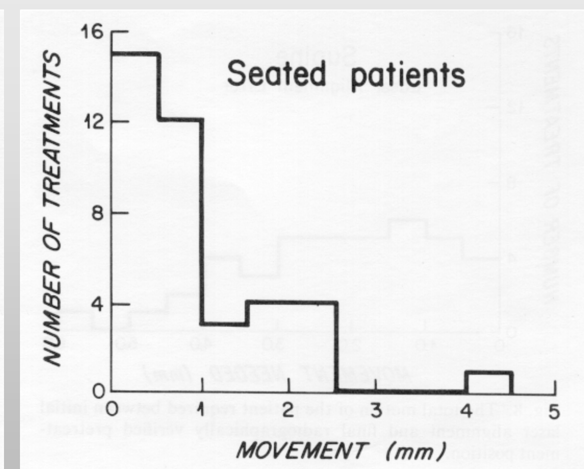
planning based on smearing tomography

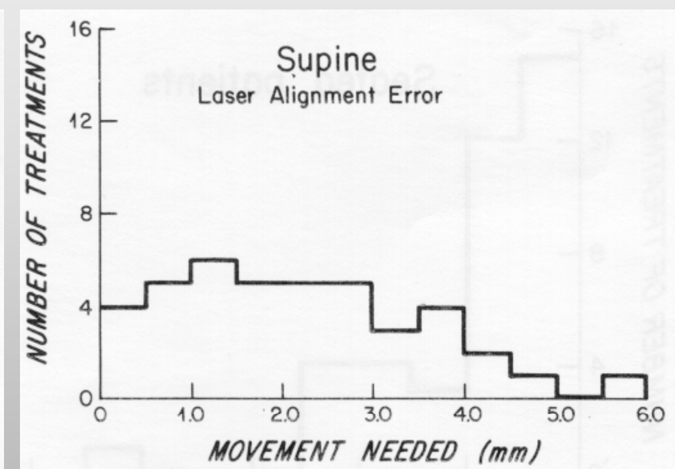
alignment based on radiographs

IMMOBILIZATION AND LOCALIZATION (contd.)







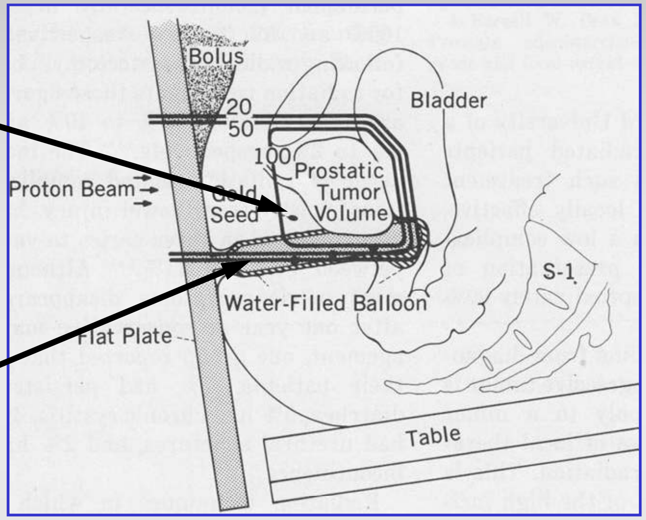


Verhey et al. Precise positioning of patients for radiation therapy. Int J Radiat Oncol Biol Phys. 1982; 8:289-294

GATING & TARGET TRACKING (intra- & inter- fraction)

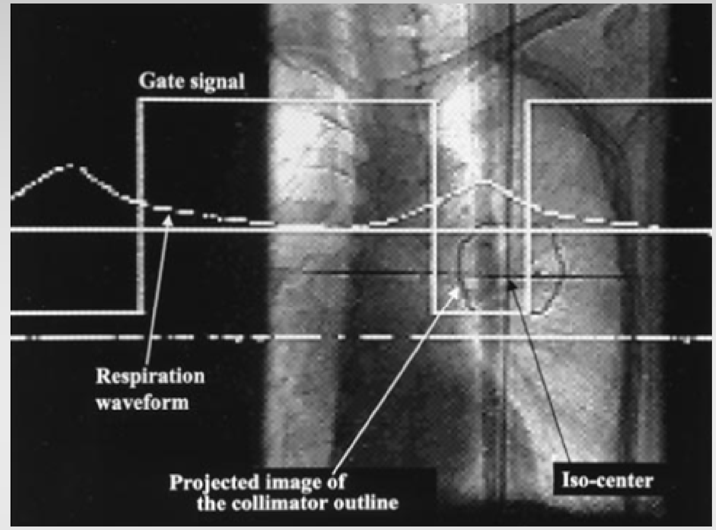
implanted gold seeds

rectal probe & water-filled balloon



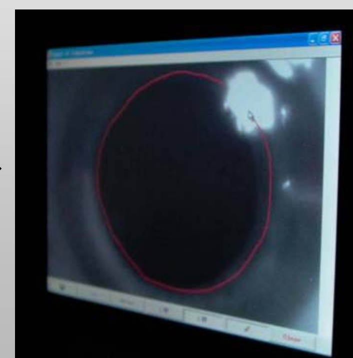
Shipley et al. Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 1979; 241:1912

respiratory gating (NIRS, Japan)



Minohara et al. Respiratory gated irradiation system for heavy-ion radiotherapy. Int J Radiat Oncol Biol Phys 47(4):1097–1103;2000

ocular tumor tracking though real time video tracking of anterior eye position (HCL, PSI)

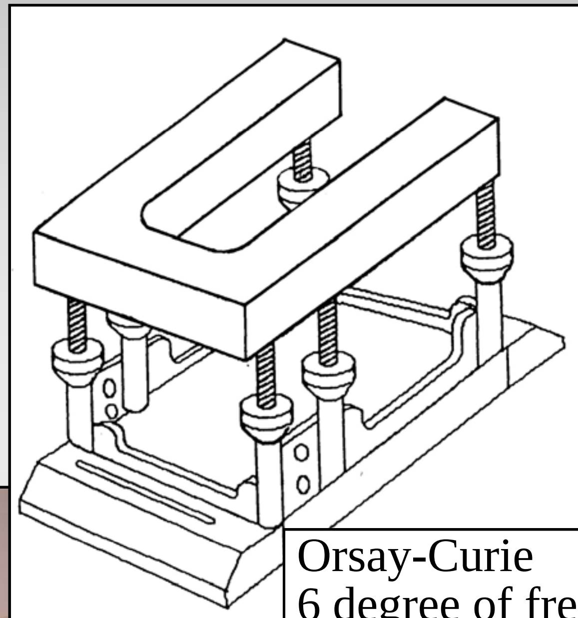


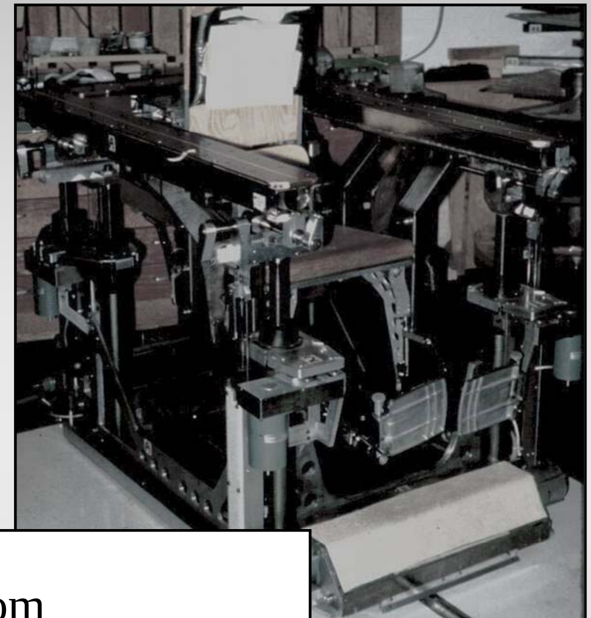
high-mag. image of anterior eye with the position of the pupil being outlined.

picture courtesy J Vervey, PSI

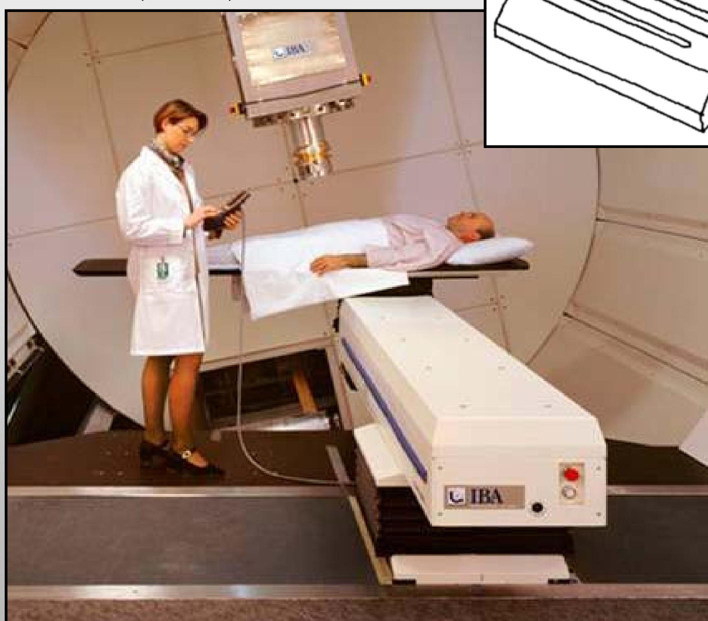
PATIENT SUPPORT ASSEMBLY

HCL 6-degree of freedom patient supporter (Wagner)

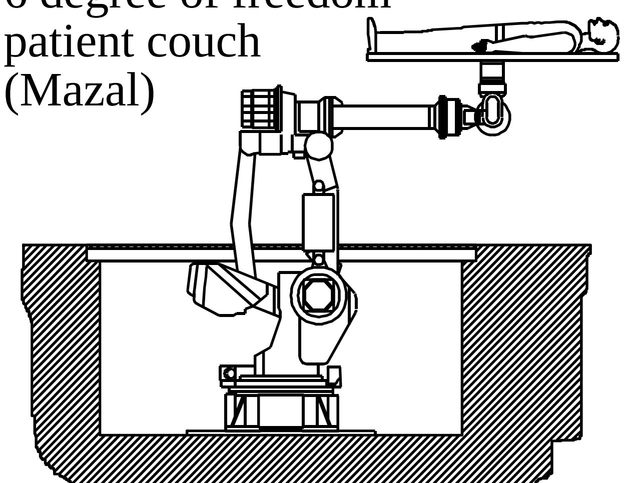




Commercial 6 degree of freedom patient couch (IBA)



Orsay-Curie 6 degree of freedom patient couch (Mazal)



The additional degrees of freedom are required to adjust for small rotational misalignments of the patient.

THROUGHPUT

- Currently it generally takes too long, and is too hard, to set up and treat a patient.
  - this is hard on the patient
  - this is hard on the staff

  tends to reduce accuracy

  - it can degrade quality, and it reduces throughput and hence increases costs
- One partial solution is to perform the patient setup outside the treatment room and bring him or her into the treatment room when it becomes available without, in principle, the need for further localization, à la PSI.

- But, this does not get at the root of the problem which is:
  inadequate systems engineering – and inadequate specification of the needs

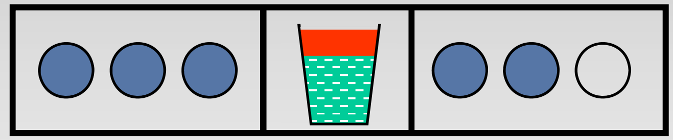
INTEGRATION

- Integration and Workflow are concepts which are more talked about than put into practice.

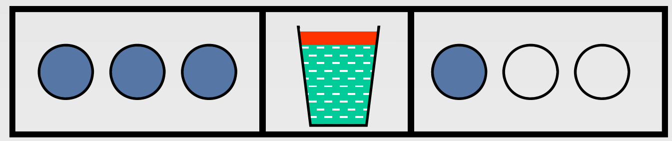
PATIENT HANDLING AND INTEGRATION

- patient handling

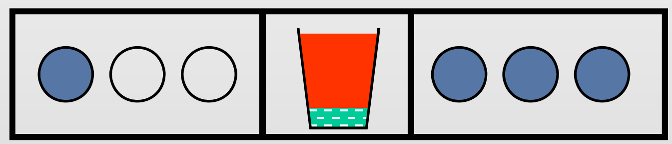
  immobilization and motion management



  patient support assembly

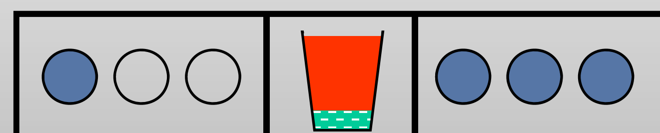


  throughput



- integration

  workflow



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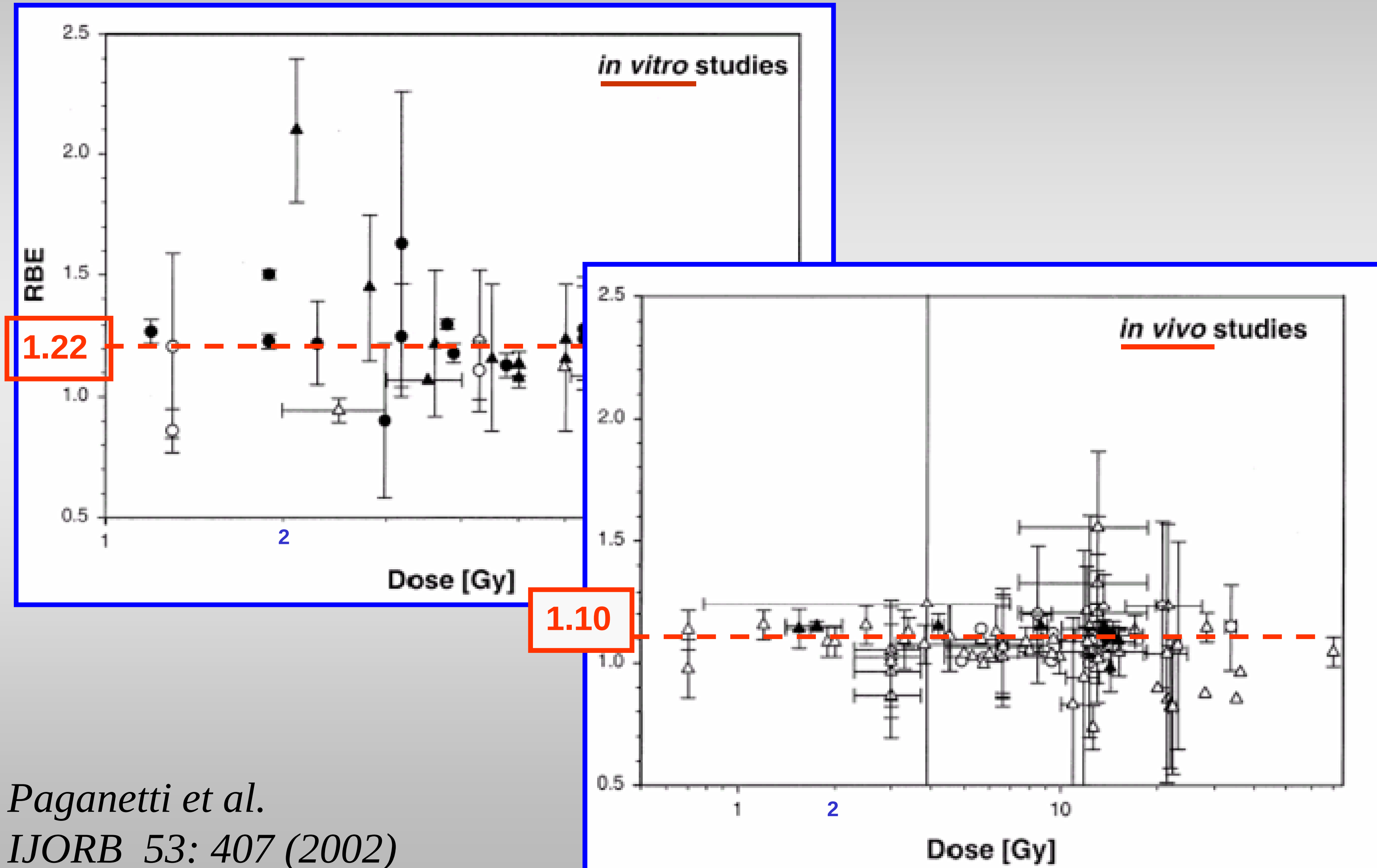
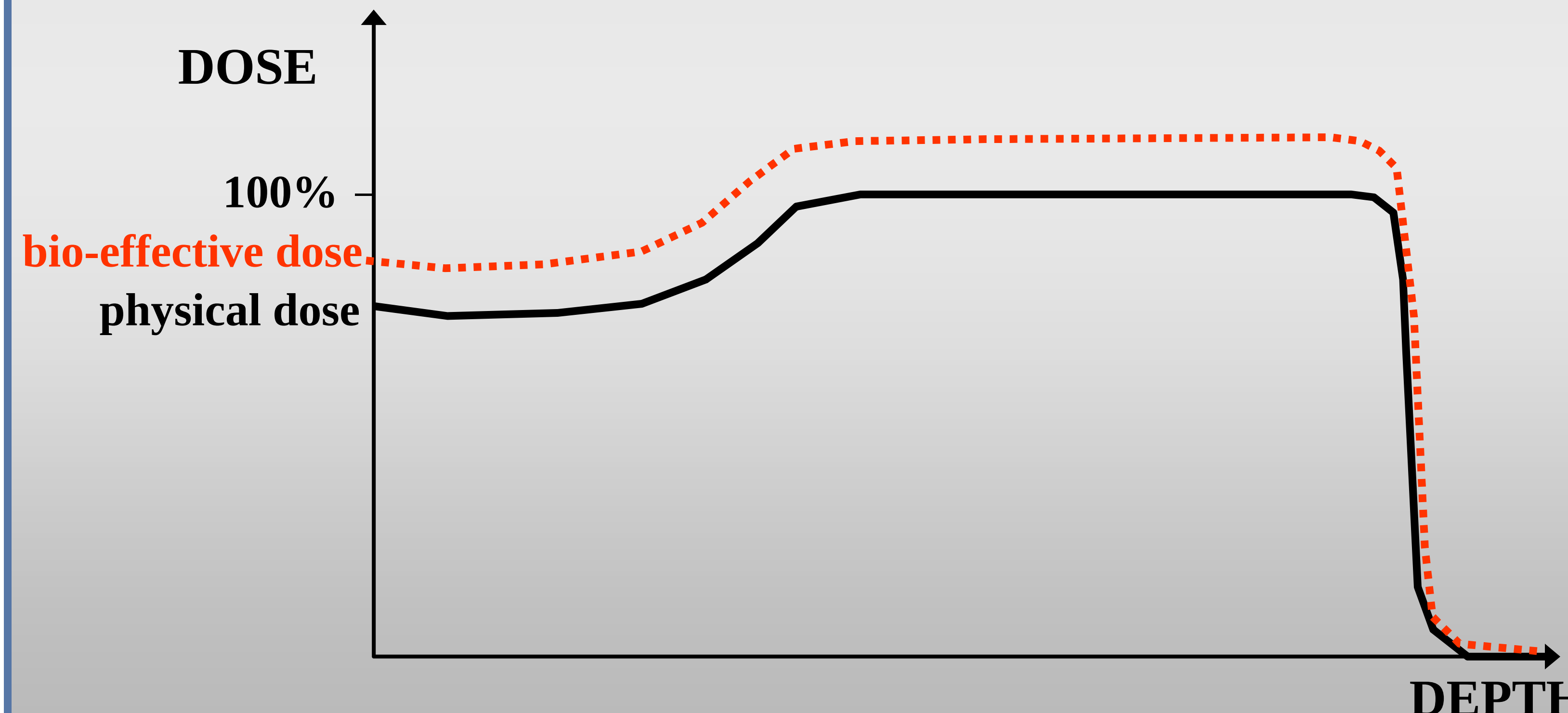
Synopsis

1. Physics
   - interactions of protons with matter
   - treatment planning
2. Technology
   - beam generation, shaping and delivery
   - patient handling
   - integration
3. Radiobiology
   - RBE
   - modelling and treatment strategy
4. Clinical Application
   - clinical experience
   - clinical trials

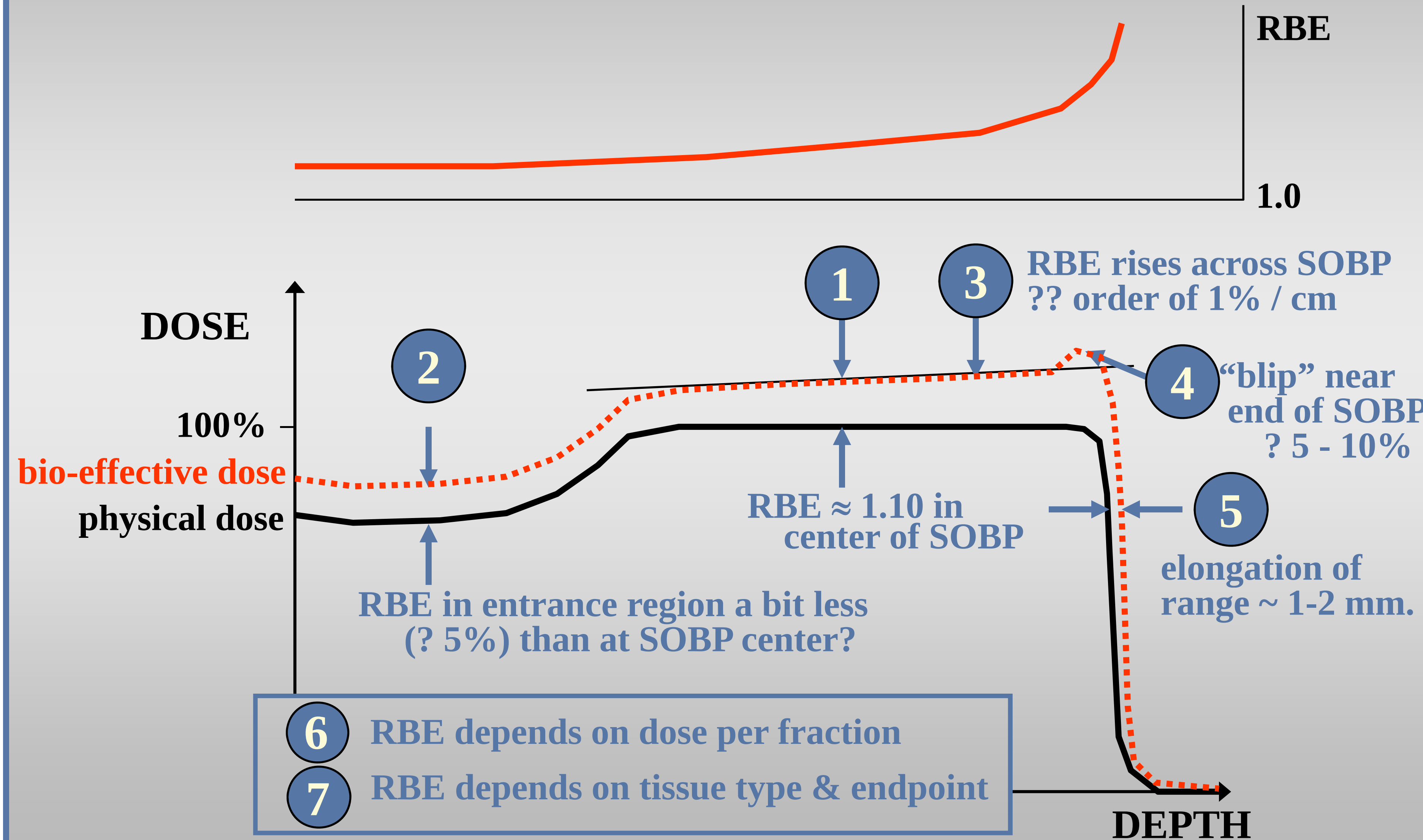
RBE = 1.10 isn't all that bad...



Paganetti et al.
IJORB 53: 407 (2002)


DOSE
100%
bio-effective dose
physical dose
DEPTH

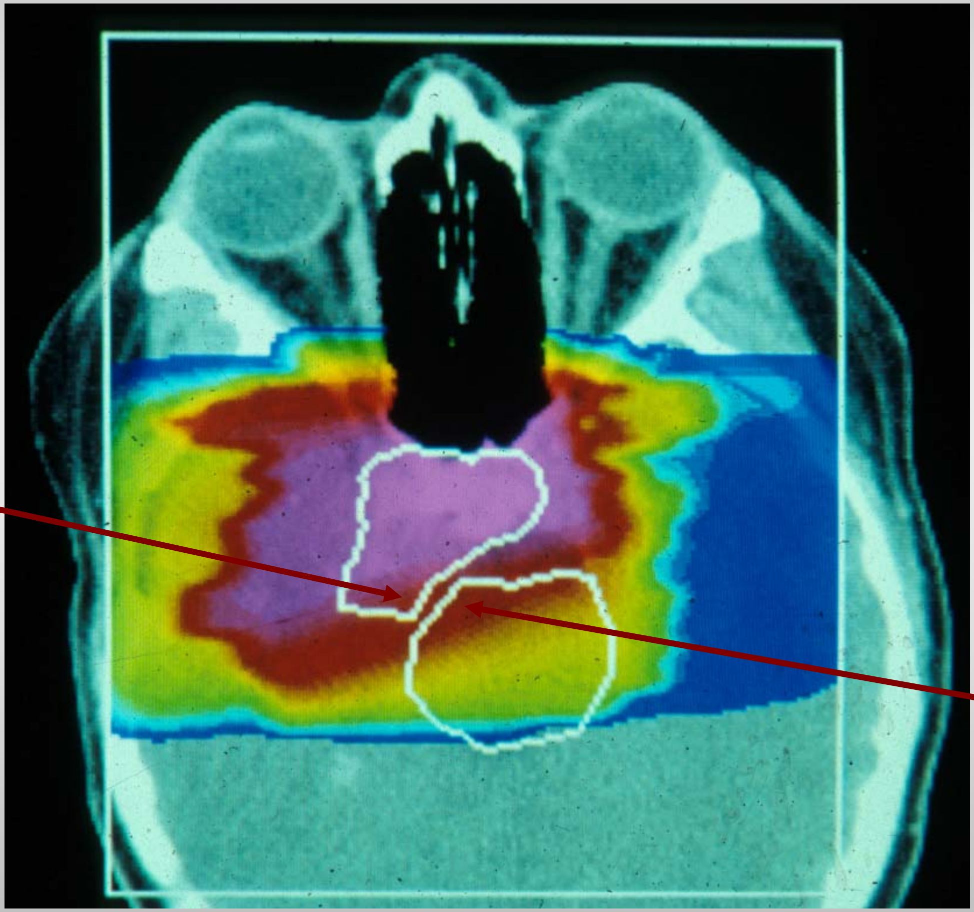
But, proton RBE needs (some) refinement



6 RBE depends on dose per fraction

7 RBE depends on tissue type & endpoint

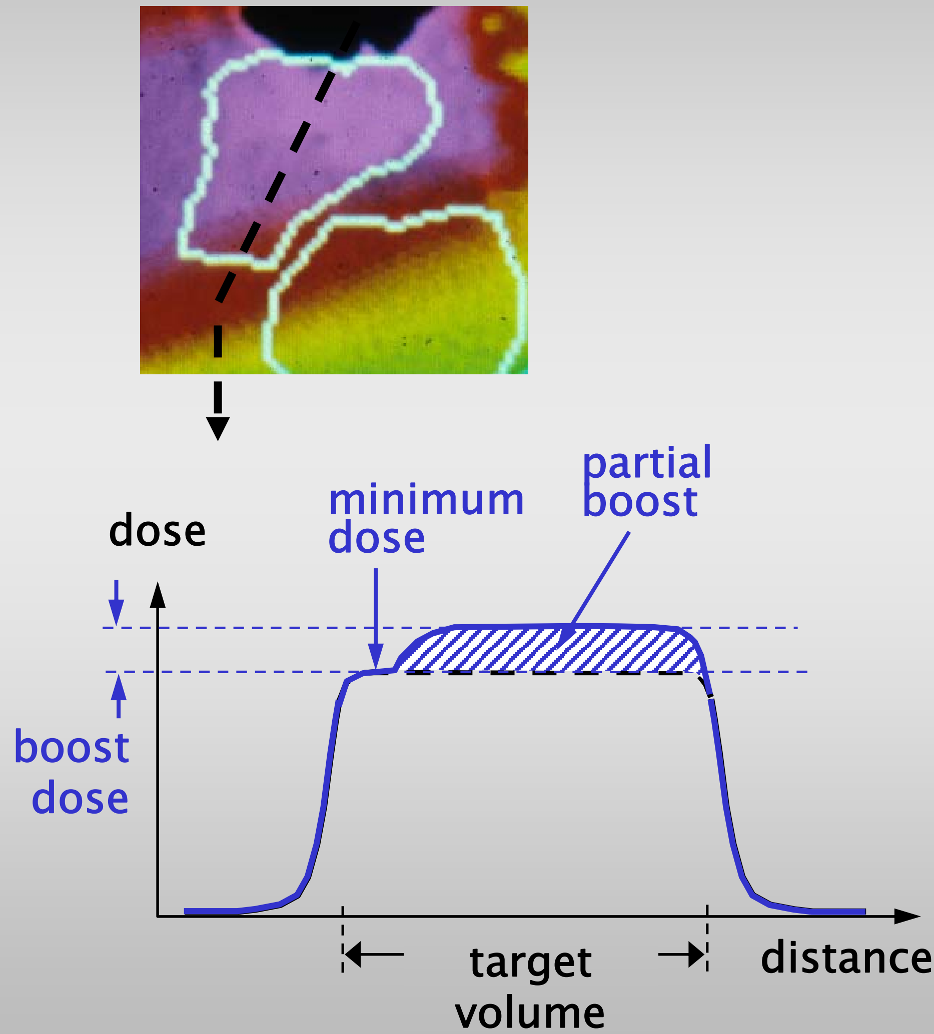
MODELLING AND TREATMENT STRATEGY



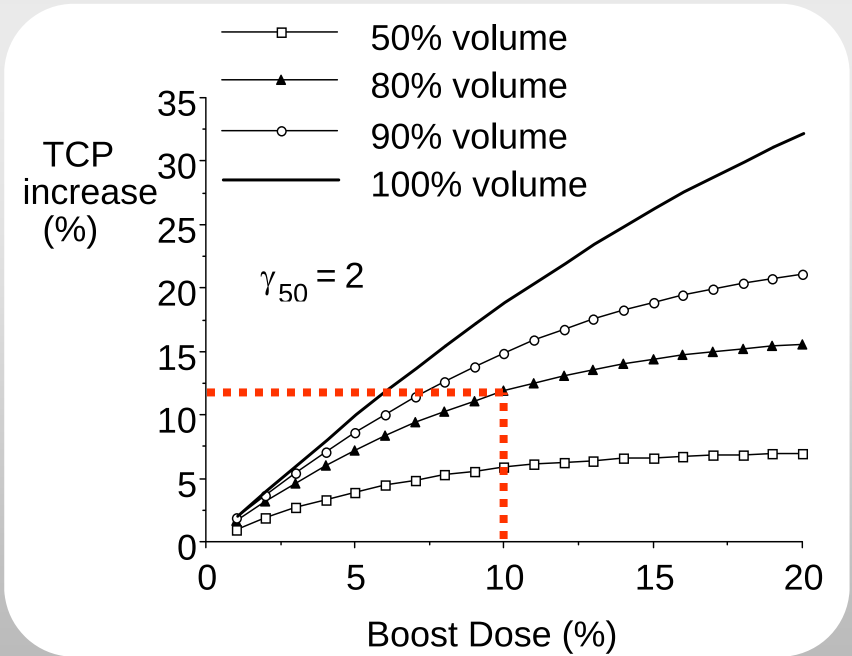
reduced tumor dose in the region in which the tumor is close to the brainstem

increased brainstem dose accepted in the small region in which it is close to the tumor

MODELLING TUMOR CONTROL PROBABILITY (TCP)

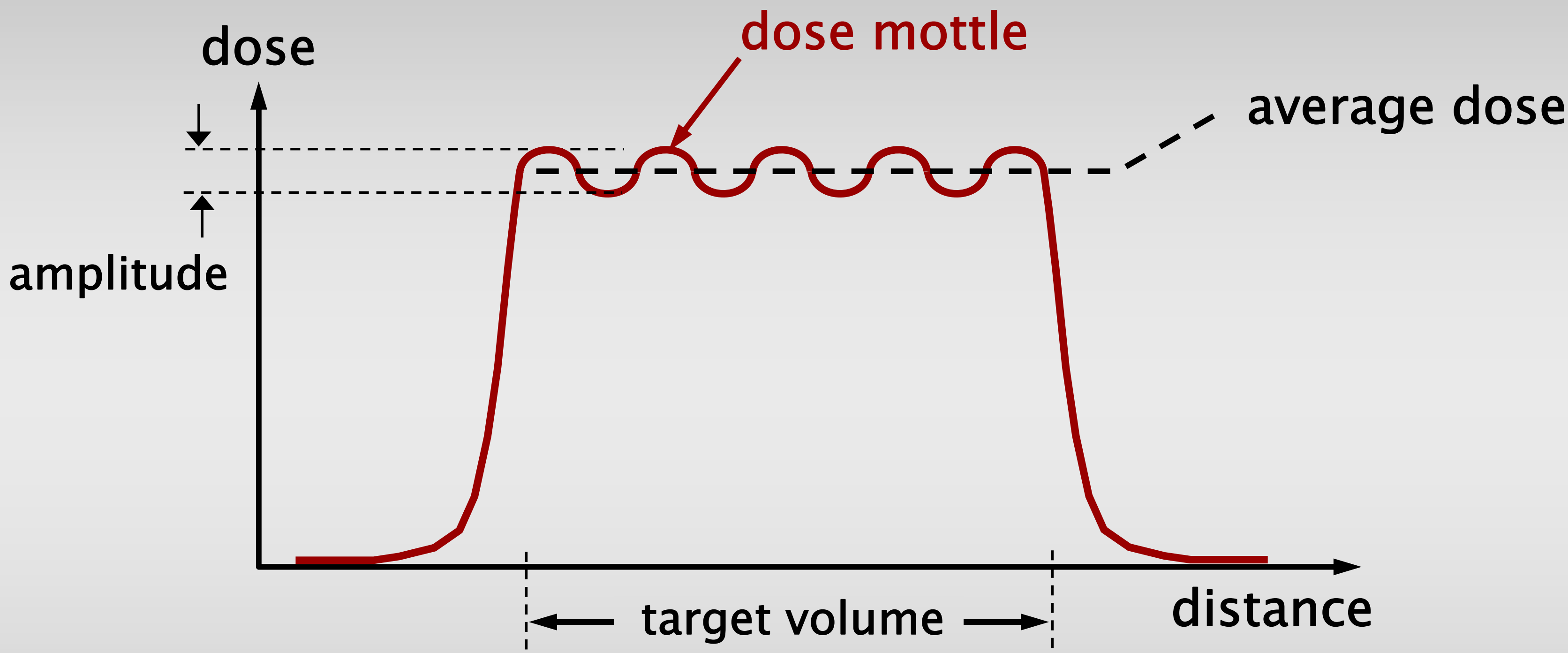


The development of biophysical models suggested that, for example, a partial boost to a tumor may increase the TCP



Goitein et al. Proceedings of the 19th LH Gray Conference (Brit. J. Radiol.). 1997: 25-39

BUT (as seen in IMRT and with interplay effects)…
BEWARE DOSE MOTTLE!



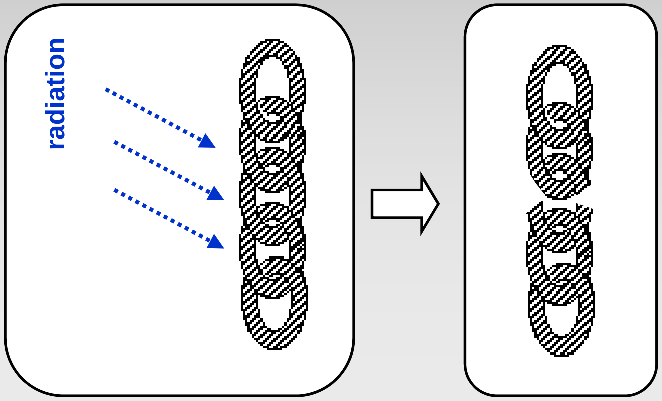
TCP (actual dose distribution < TCP (average tumor dose)

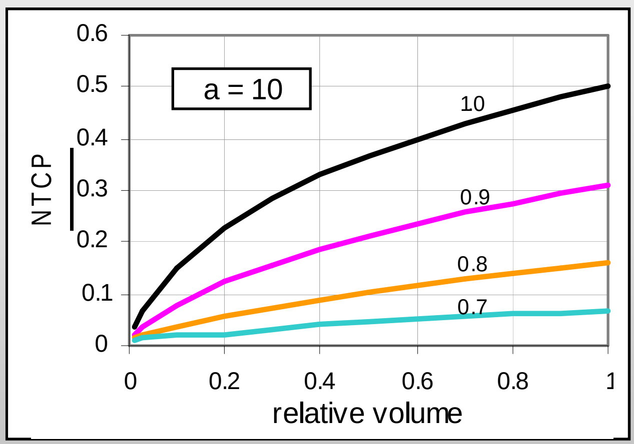
for a dose mottle of ±7.5%   ΔTCP ≈ – 4 %
for a dose mottle of ±10%   ΔTCP ≈ – 6.5 %

Brahme A. Acta Radiol Oncol 23: 379-391 (1984)

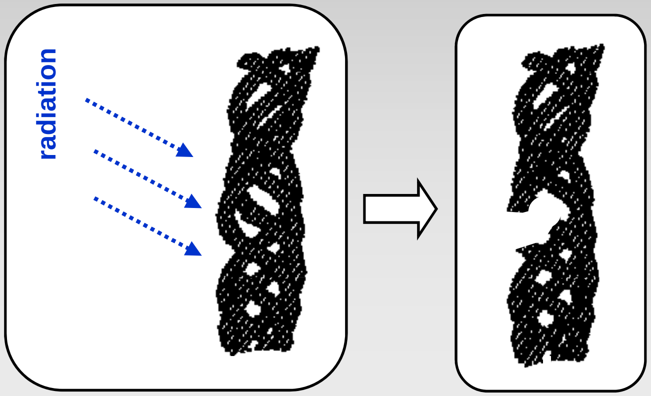
MODELLING NORMAL TISSUE COMPLICATION PROBABILITY (NTCP)

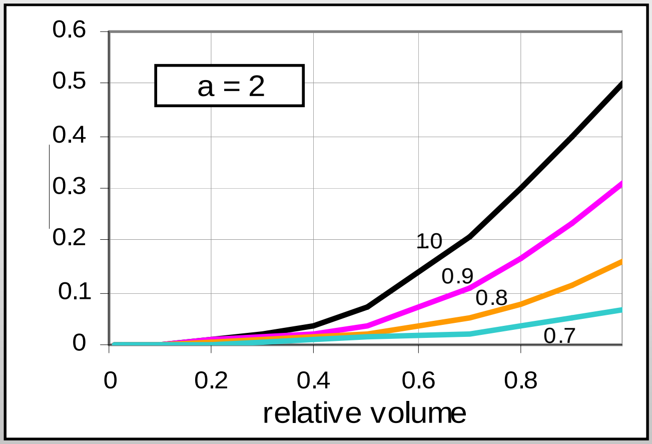
serial structure





parallel structure

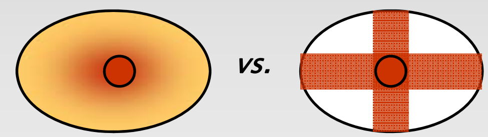




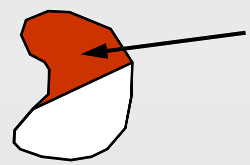
Modelling supported the idea that organs could tolerate a higher dose if it was only delivered to part of the organ.

RADIOBIOLOGY: dose-volume effects

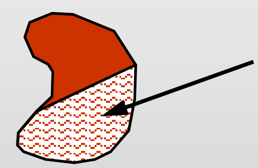
- There are many important but unanswered questions
  - the answers to which are relevant for all radiations, but particularly to particles with which one is attempting to spare normal tissues particularly effectively
- Some of the unsolved issues are:
  - “bath-or-shower dilemma” (is it better to deliver a lower dose to a larger volume of normal tissue, or a higher dose to a smaller volume?)



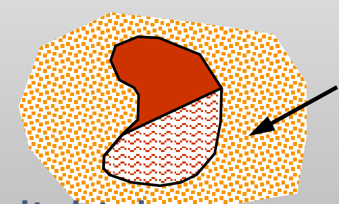
  - how does functional damage to an organ or tissue depend on the relative (or absolute) volume irradiated to high dose?



  - how does functional damage to an organ or tissue depend on the (lower) dose delivered to the rest of the volume?



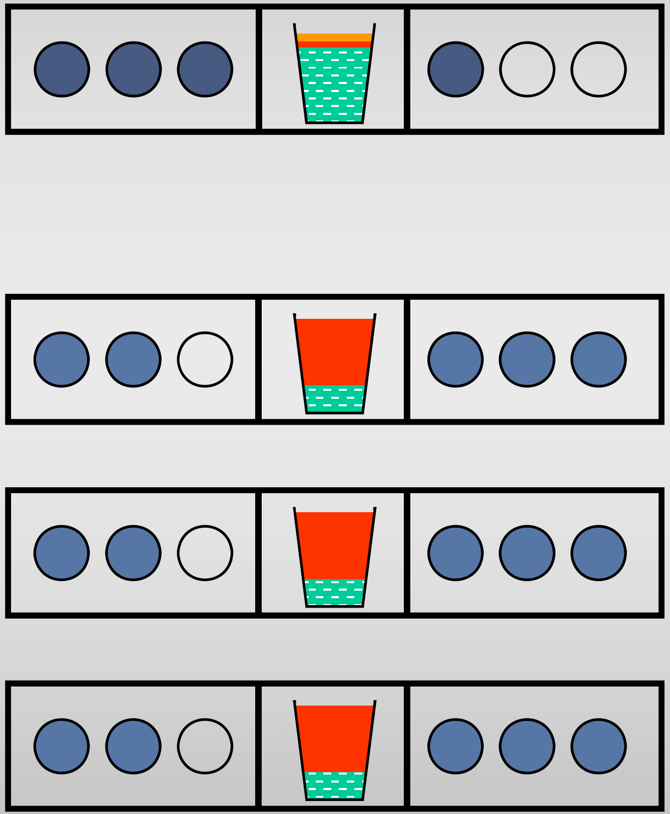
  - how does the radiation damage of an organ or tissue depend on the radiation experience of nearby tissues and organs?



- We need to resurrect whole-organ and whole-organism radiobiology
- When we know the answers to some of these questions, we will need new biophysical models so we can use computers to optimize treatments

RBE, MODELLING AND TREATMENT STRATEGY

- RBE
- Radiation response of tissues
    - data
    - modelling
    - treatment strategies



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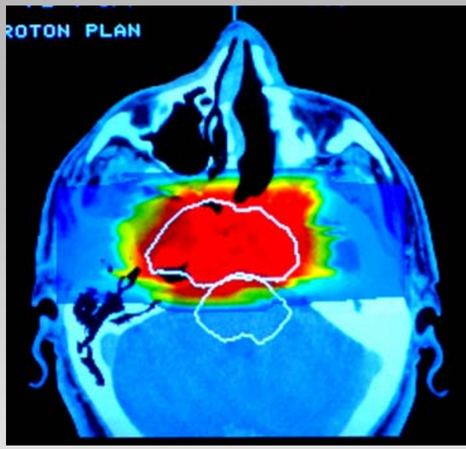
CLINICAL EXPERIENCE

- Some 61,000 patients have been treated with proton beam therapy as of Feb. 2009.
- The largest single group is comprised of ~17,000 patients with ocular melanomas.

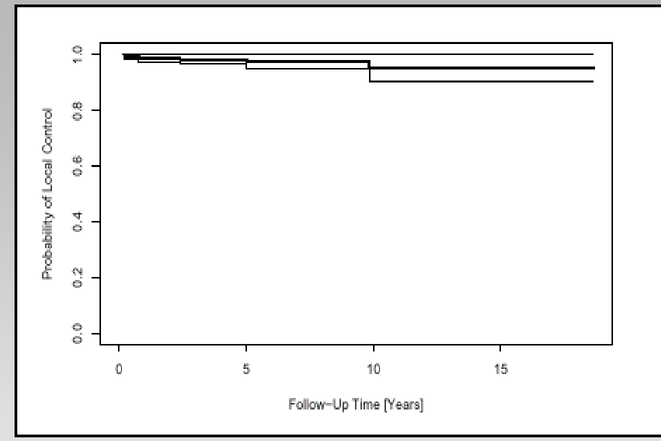
http://ptcog.web.psi.ch/patient_statistics.html

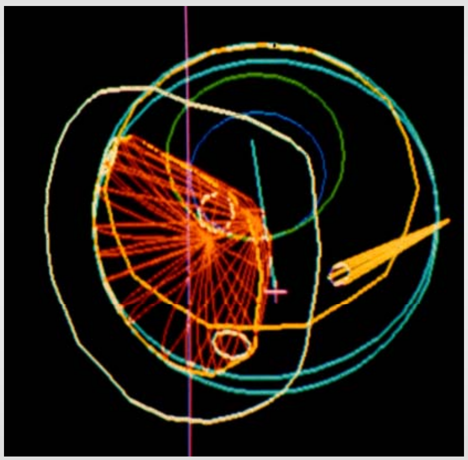
- There have been only a limited number of clinical trials of proton beam therapy, and only two randomized clinical trials of protons vs. conventional radiotherapy.
- The experience to date should perhaps be read as a confirmation that the theoretical arguments for proton beam therapy have been upheld in the limited number of situations in which they have been tested.

Goitein & Goitein. Swedish protons. Acta Oncol. 2005;44(8):793-7

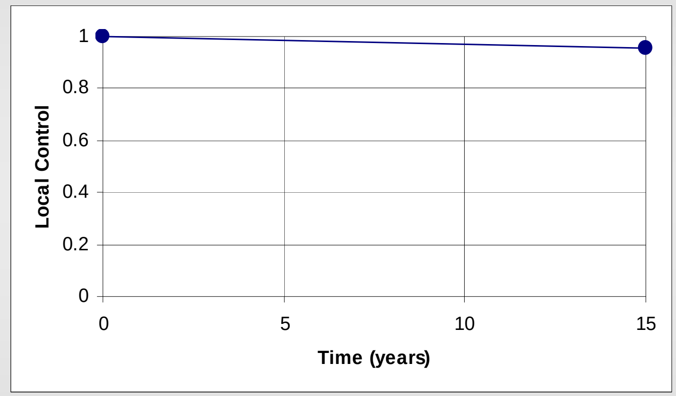


Chondrosarcoma - local control



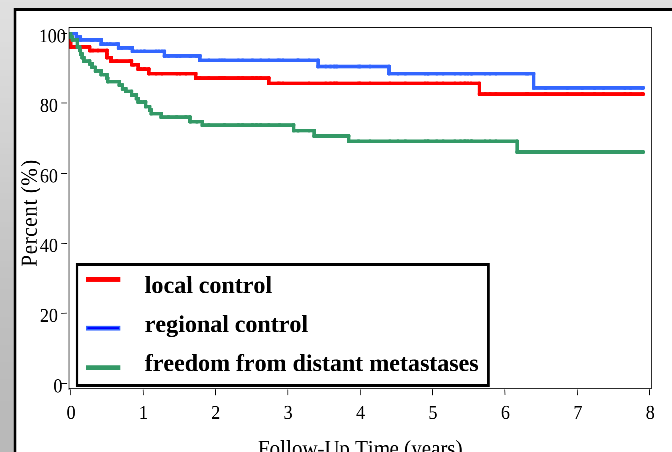


Choroidal melanoma - local control



Paranasal sinus tumors

33 squamous cell carcinomas,
30 carcinomas with neuroendocrine differentiation
20 adenoid cystic carcinomas
13 soft tissue sarcomas, and
6 adenocarcinomas.
The median dose was 71.6 CGE.



THE RATIONALE FOR JUDGING THE CLINICAL SUPERIORITY OF PROTONS VIS-À-VIS X-RAYS

- For the same dose to the target volume, protons deliver a lower physical dose to the uninvolved normal tissues than do high-energy X-rays.
- There is very little difference in tissue response per unit dose between protons of therapeutic energies as compared with high-energy X-rays, so that the only relevant differences are physical.
- There is no medical reason to irradiate any tissue judged not to contain malignant cells.
- Radiation damages normal tissues and the severity of that damage increases with increasing dose.

Suit H, et al. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. Radiother Oncol. 2008;86:148–153

Each of these 4 statements is established experimentally beyond reasonable doubt

RANDOMIZED CLINICAL TRIALS

- There are two fundamental principles which govern whether a randomized clinical trial (RCT) is ethically appropriate:

  The arms of the study must be in equipoise. That is to say, the arms must be judged to be substantially equivalent from a patient's point of view.

  When a doctor agrees to take care of a patient, he or she is entering into an unwritten contract with the patient to use his or her best efforts and judgment on behalf of that patient. There can be no unspoken reservation that societal interests may take priority over those of the patient, and the patient may expect to be fully informed regarding any facts that he or she might deem relevant.

These principles, together with the previous 4 statements, mean that <u>many otherwise desirable RCTs can not be performed for ethical reasons</u> - equipoise can not truthfully be said to obtain for them.

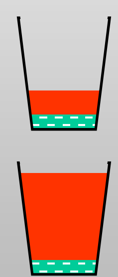
CLINICAL TRIALS (contd.)

- It is a great pity that almost no case-controlled clinical studies have been planned or performed.
- It would seem that, in the absence of an ability in many cases to conduct randomized clinical trials, carefully designed prospective case-controlled comparisons between proton centers and institutions lacking a proton capacity would be desirable.

- clinical trials

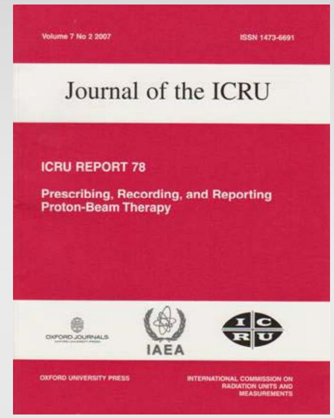
  randomized

  case-controlled

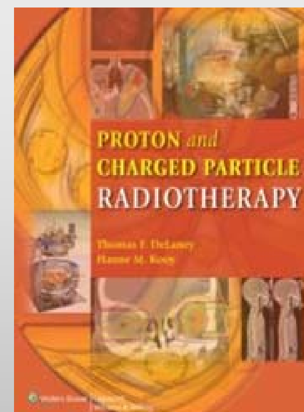


RECENT TEXTS

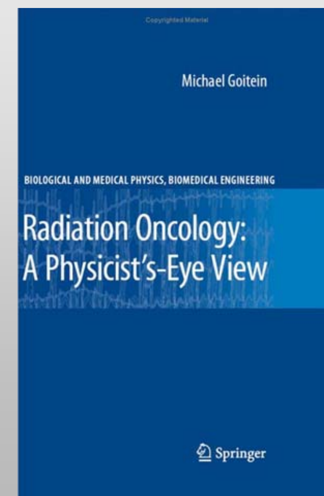
- Gottschalk B (2004) “Passive Beam Spreading in Proton Radiation Therapy” http://huhepl.harvard.edu/~gottschalk/
  File named “pbs.pdf” can be extracted from BGdocs.zip
  See, also, PowerPoint lectures in BGtalks.zip



- ICRU report 78 “Prescribing, Recording and Reporting Proton Beam Therapy” Oxford U. Press. Journal of the ICRU 7(2); 2007



- T.F. Delaney and H.M. Kooy (eds) “Proton and Charged Particle Radiotherapy” Lippincott Williams and Wilkins, 2007



- M. Goitein “Radiation Oncology: A Physicist’s-Eye View” Springer, 2007

SUMMARY

INTERACTIONS OF PROTONS

proton penetration

Coulomb scattering

nuclear interactions

dosimetry

inhomog- -eneities

TREATMENT PLANNING

use of imaging

image registration

changes with time

broad- & pencil-beam algorithms

Monte Carlo dos[e] calculation

uncertainties: calcn. and allowance for

IMPT: understanding

IMPT: solutions

optimization: search techniques

optimization: dose-based

optimization: biology-based

robust optimization

TECHNOLOGY

current sources of protons

future sources of protons

scattered beam technology

scanned beam technology & IMPT

scattered beam: depth characteristics

scanned beam: depth characteristics

scattered beam: lateral penumbra

scanned beam: lateral penumbra

immobilization & motion management

patient support systems

throughput, integration & workflow

RADIOBIOLOGY

RBE value(s)

tissue response: data

tissue response: models

treatment strategies based on biology

CLINICAL TRIALS

randomized protons vs. X-rays

case-controlled protons vs. X-rays

CONCLUSIONS

- Much has been done.
- Much remains to be done.
- It is important that what has been learned in the past be incorporated into the clinical work of the future – and not simply regarded as being of purely historical interest and hardly worth learning about.

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