

RADIOBIOLOGIA (AA 2010-2011)

**UNIVERSITÀ DEGLI STUDI DI CAGLIARI
Facoltà di Medicina e Chirurgia
SCUOLA DI SPECIALIZZAZIONE IN FISICA MEDICA**

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**Parte 14
Basi radiobiologiche dell'adroterapia**

L'adroterapia

Adroterapia:

Moderna tecnica di radioterapia (principalmente oncologica) che utilizza radiazioni adroniche (principalmente cariche)

adroni = particelle non elementari costituite da quark

esempi di adroni carichi: protoni, ioni più pesanti

esempi di adroni neutri: neutroni

Il termine **adroterapia** fu utilizzato da Ugo Amaldi e coll., ed accettato in pratica nel 1993 con il 1st Int. Symposium on Hadrontherapy a Como.

L'inizio dell'adroterapia

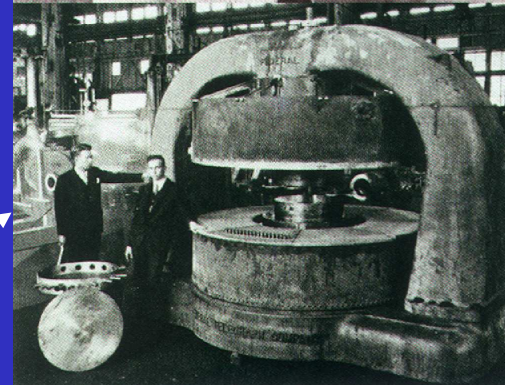
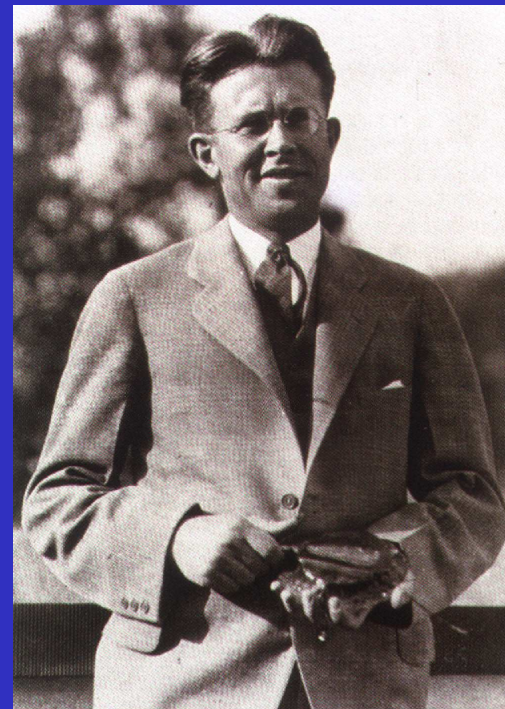
Il primo ciclotrone fu costruito da Ernest Lawrence nel 1930 a Berkeley.

Negli anni seguenti, egli ed i suoi collaboratori costruirono ed usarono ciclotroni per produrre neutroni veloci per il trattamento di tumori (successivamente sospeso)

La protonterapia fu proposta da Robert Wilson nel 1946.

Negli anni seguenti a Berkeley furono impiegati fasci di protoni per trattamenti clinici

Ernest Lawrence ad un Congresso della Natl. Acad. Sciences a Berkeley. Foto presa il 19 settembre 1930



Il ciclotrone da 27" nel 1932

L'adroterapia in Italia

Nella nostra nazione oggi l'adroterapia è una realtà:

- CÀTANA (INFN-LNS, Catania)
- CNAO (Pavia) in costruzione
- altre prospettive

Ciò si deve principalmente a due fatti:

- Il lavoro pionieristico del Progetto Adroterapia e della Fondazione TERA del Prof. Ugo Amaldi
- La decisione dell'INFN di partecipare attivamente allo sviluppo dell'adroterapia.

Proton and Carbon ion Therapy Facilities

in operation (*PTCOG, January 2007*)

North America = 8

Europe = 11 + 1

Japan = 7 + 2

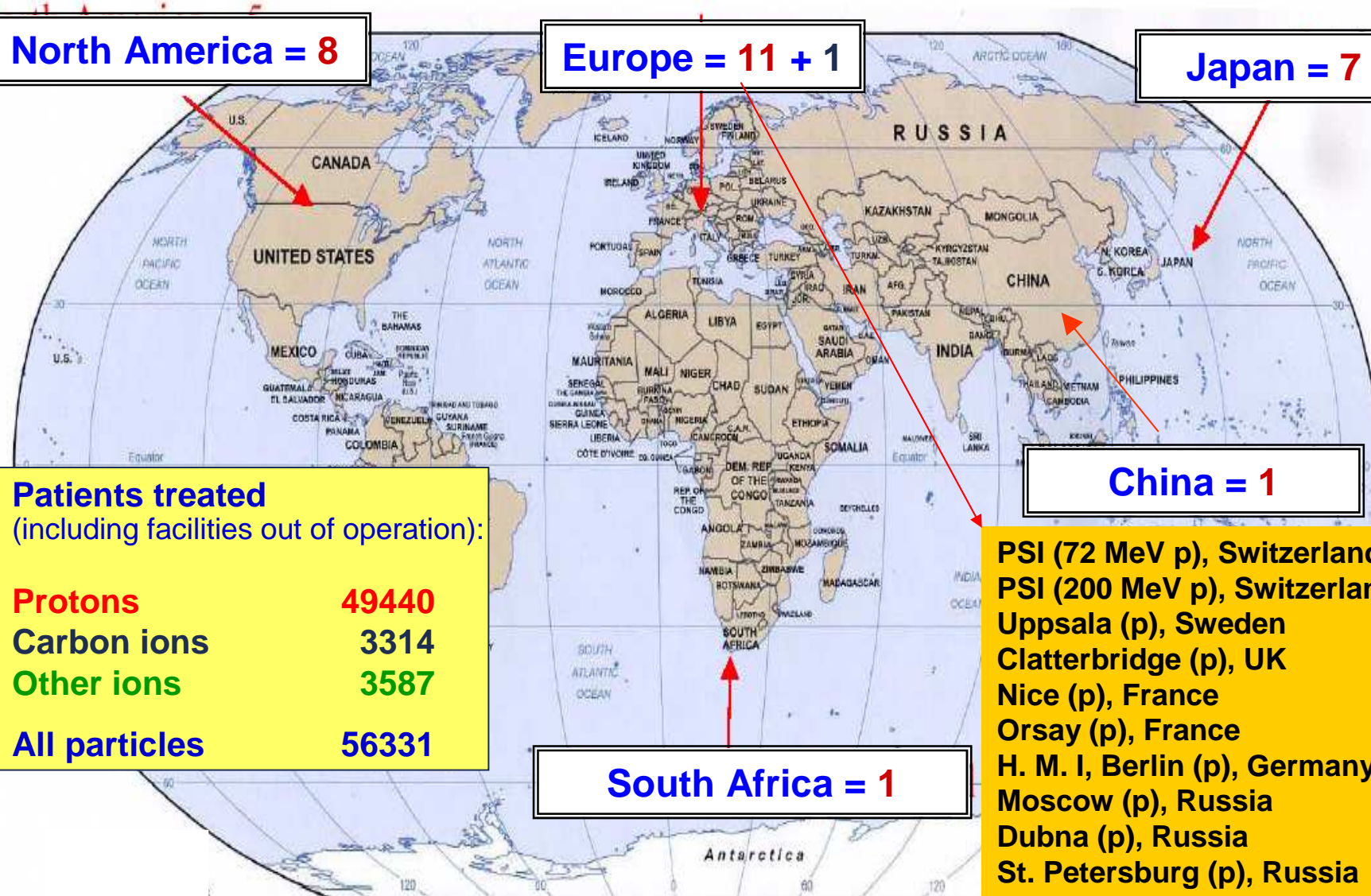
Patients treated
(including facilities out of operation):

Protons	49440
Carbon ions	3314
Other ions	3587
All particles	56331

South Africa = 1

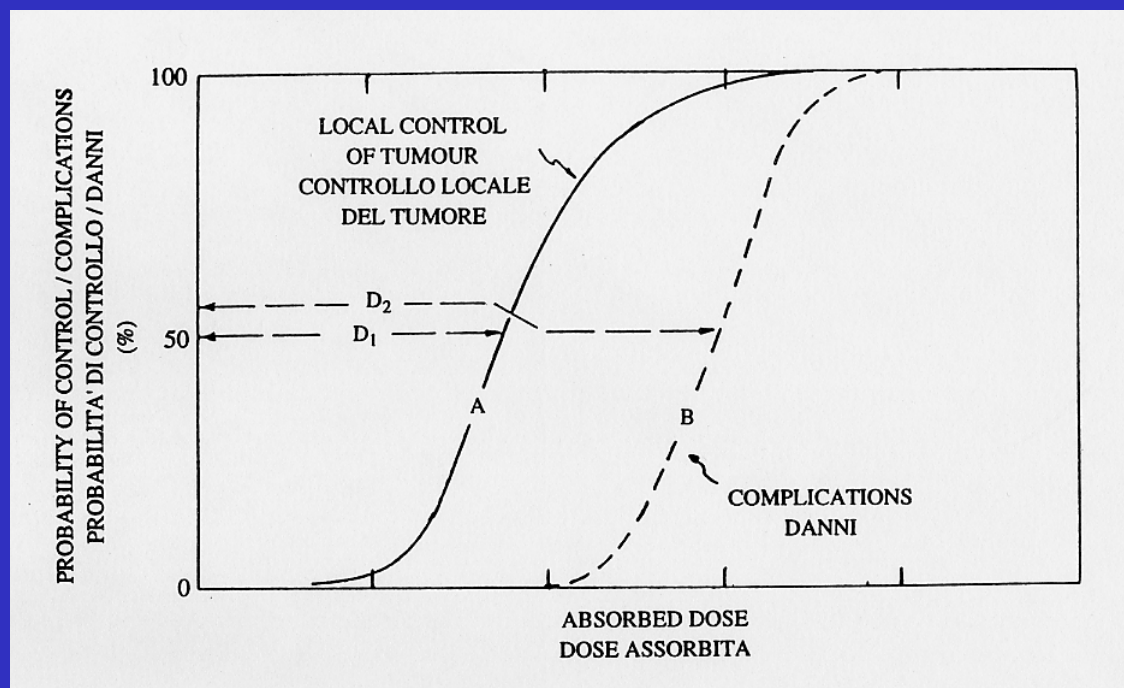
China = 1

PSI (72 MeV p), Switzerland
 PSI (200 MeV p), Switzerland
 Uppsala (p), Sweden
 Clatterbridge (p), UK
 Nice (p), France
 Orsay (p), France
 H. M. I, Berlin (p), Germany
 Moscow (p), Russia
 Dubna (p), Russia
 St. Petersburg (p), Russia
 INFN-LNS (p) Catania, Italy
 G.S.I. Darmstadt (C), Germany



Obiettivi della radioterapia

Fornire al "bersaglio" una dose tanto alta da distruggerlo mantenendo al tempo stesso la dose ai tessuti circostanti, inevitabilmente irradiati, entro limiti tali da non comportare complicazioni e danni gravi o irreversibili.



Rapporto Terapeutico: rapporto tra la dose D_2 corrispondente al 50% di probabilità di fare danni e la dose D_1 corrispondente al 50% di probabilità di ottenere il controllo locale del tumore.

Crescente interesse per la terapia con adroni carichi (in particolare protoni e ioni carbonio)

BASI RAZIONALE

Possibilità di depositare una dose nel tumore in maniera più selettiva rispetto alle radiazioni convenzionali
(grazie alla distribuzione d'energia su scala **macroscopica**) .

Vantaggiose caratteristiche biofisiche e radiobiologiche, che possono essere sfruttate per ottenere ulteriori vantaggi terapeutici
(legate alla distribuzione d'energia su scala **microscopica**).

Increasing interest in hadrontherapy

PHYSICAL AND RADIOBIOLOGICAL REASONS

Radiations differing in type and energy can give energy distributions completely different on both

- **macroscopic** scale \Rightarrow **dosimetric** properties
- **microscopic** scale \Rightarrow **radiobiological** properties

X- and γ -rays = **sparsely** ionizing radiation

Protons (at low E) and carbon ions = **densely** ionizing radiation

Basi biofisiche e radiobiologiche dell'adroterapia

PROPRIETA' CHIAVE DEI PROTONI E DI IONI PIU' PESANTI:

Fisiche/dosimetriche (distribuzione **macroscopica** dell'energia):

minore diffusione angolare, percorso definito



distribuzione di dose ben definita (picco di Bragg)

Biofisiche/radiobiologiche (distribuzione **microscopica** dell'energia):

deposizione di energia molto localizzata lungo la traccia delle particelle



danno concentrato e più complesso



aumento dell'efficacia biologica ("qualità" della radiazione)

(proprietà dipendente dall'energia delle particelle - depositi energetici tanto più localizzati quanto più l'energia è bassa)

Differenze tra varie radiazioni: profili dose-profondità

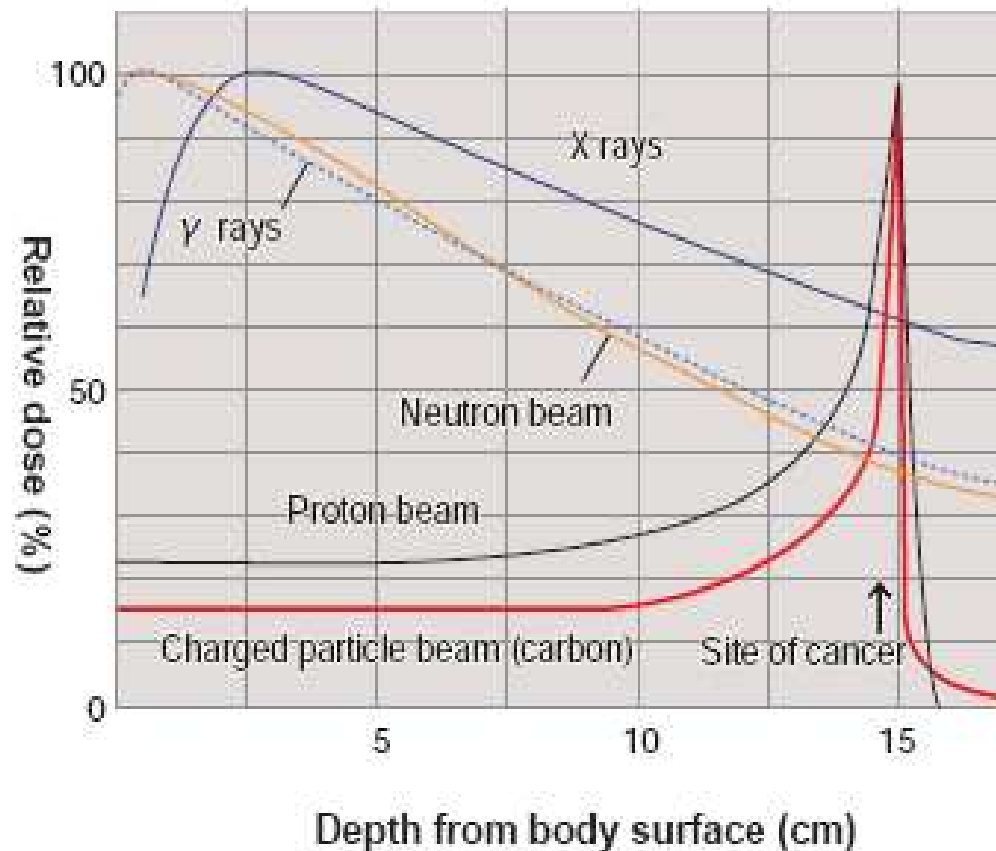
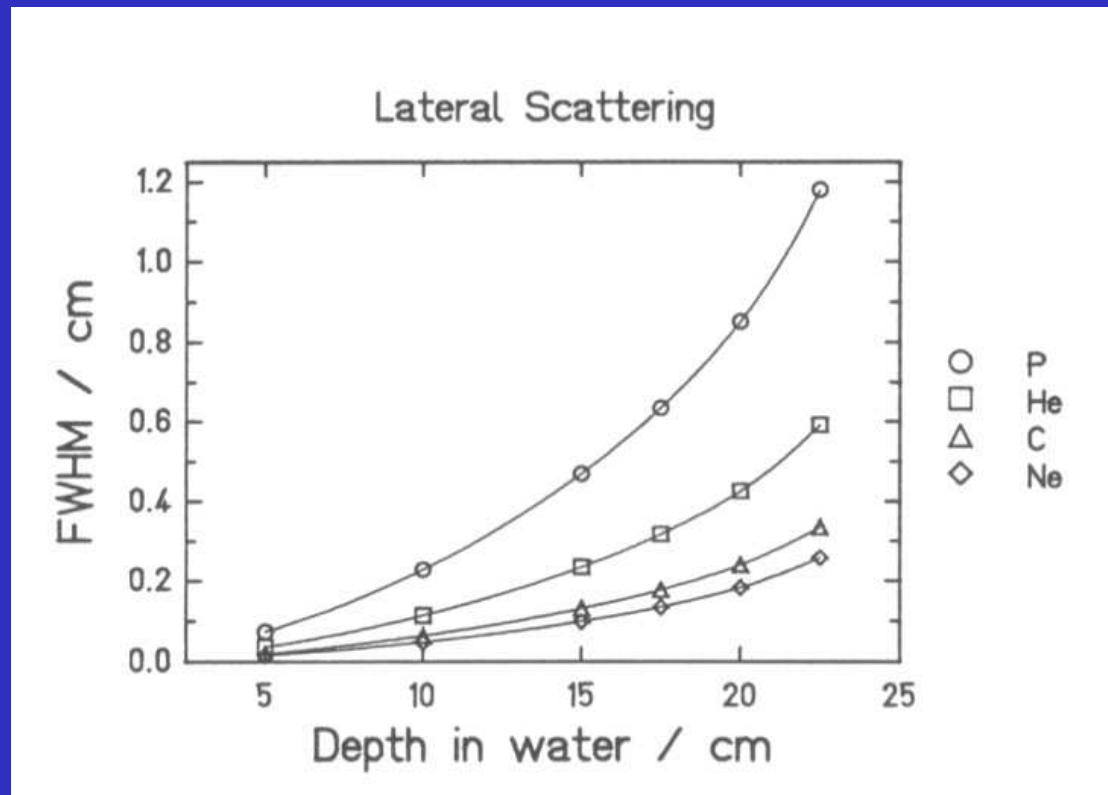


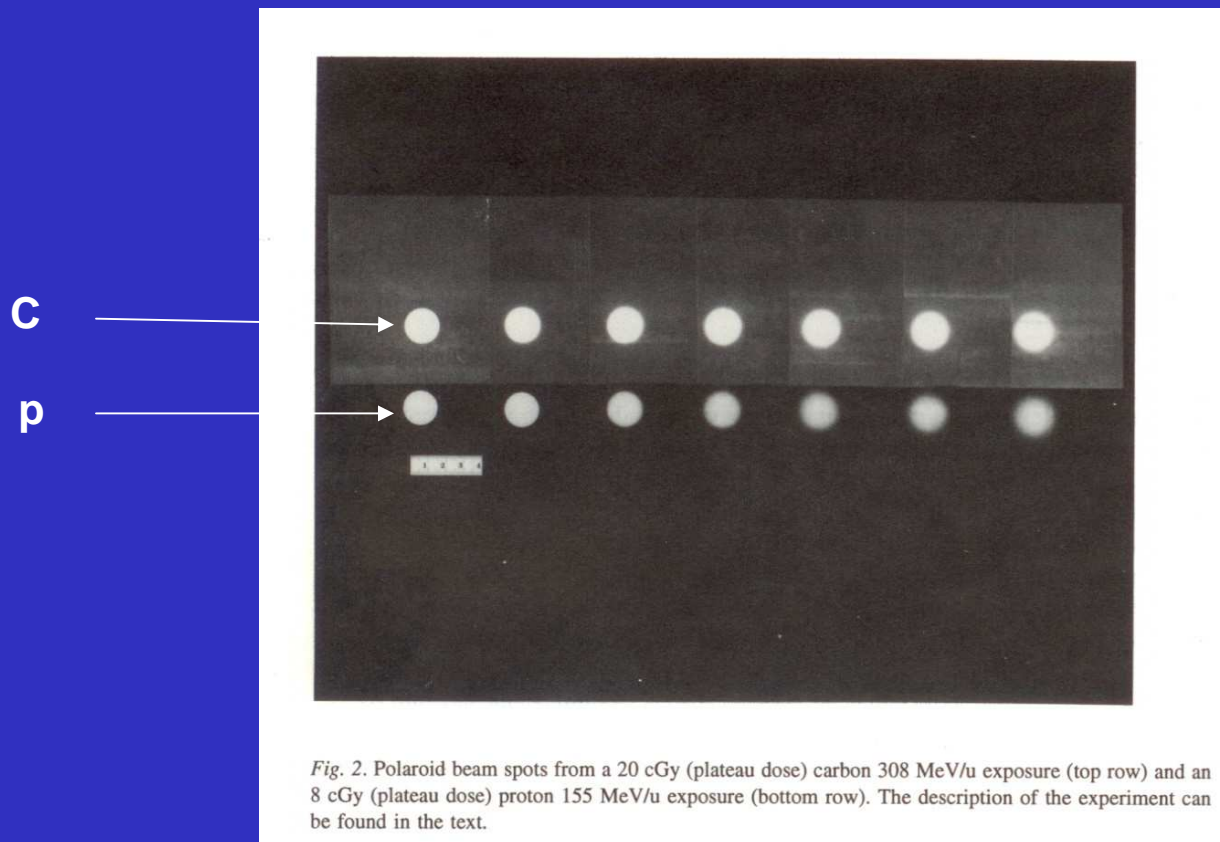
Fig. 2 Dose distribution of various types of radiation in a body

Distribuzione dell'energia su scala macroscopica: scattering laterale



from: Kraft et al 1994

Distribuzione dell'energia su scala macroscopica: scattering laterale



15 cm penetration into tissue-equivalent material; C= 308 MeV/u, p=115 MeV/u,
Top: C ions 20 cGy; bottom: p 8 cGy
Left: entrance channel; right: Bragg peak
(from: Blakely 1994)

L'inizio della radiobiologia adronica

Sin dagli inizi dell'adroterapia gli studi sulle proprietà biofisiche e radiobiologiche degli adroni (carichi) sono stati strettamente connessi agli sviluppi delle applicazioni cliniche

Nel 1939 Cornelius Tobias giunse a Berkeley, dove produsse i primi fasci di ioni C accelerati e successivamente iniziò e guidò i programmi di radiobiologia con gli acceleratori di Berkeley sino al 1988

La radiobiologia adronica in Italia

Vivace ricerca in Radiobiologia degli adroni da molti anni in Italia (in pratica sin dal 1979 – v. per una review: Belli, An overview of recent charged-particle radiation biology in Italy. *Physica Medica* 17 Suppl 1, 278-282, 2001)

Varie iniziative, come la collaborazione TERA, il Progetto TOP dell'ISS, l'esperimento ATER dell'INFN, hanno avuto un ruolo catalitico e di stimolazione per la ricerca nel campo della radiobiologia delle particelle cariche.

Sono state incoraggiate aggregazioni tra vari gruppi ed è stata creata l'occasione per collegare la radiobiologia di base ad un quadro di grande interesse applicativo.

Nuova prospettiva a seguito della presenza di Centri di Adroterapia anche nel nostro Paese (1 già operante, 1 in via di realizzazione)

Fotoni e adroni carichi: differenze importanti nell'adroterapia

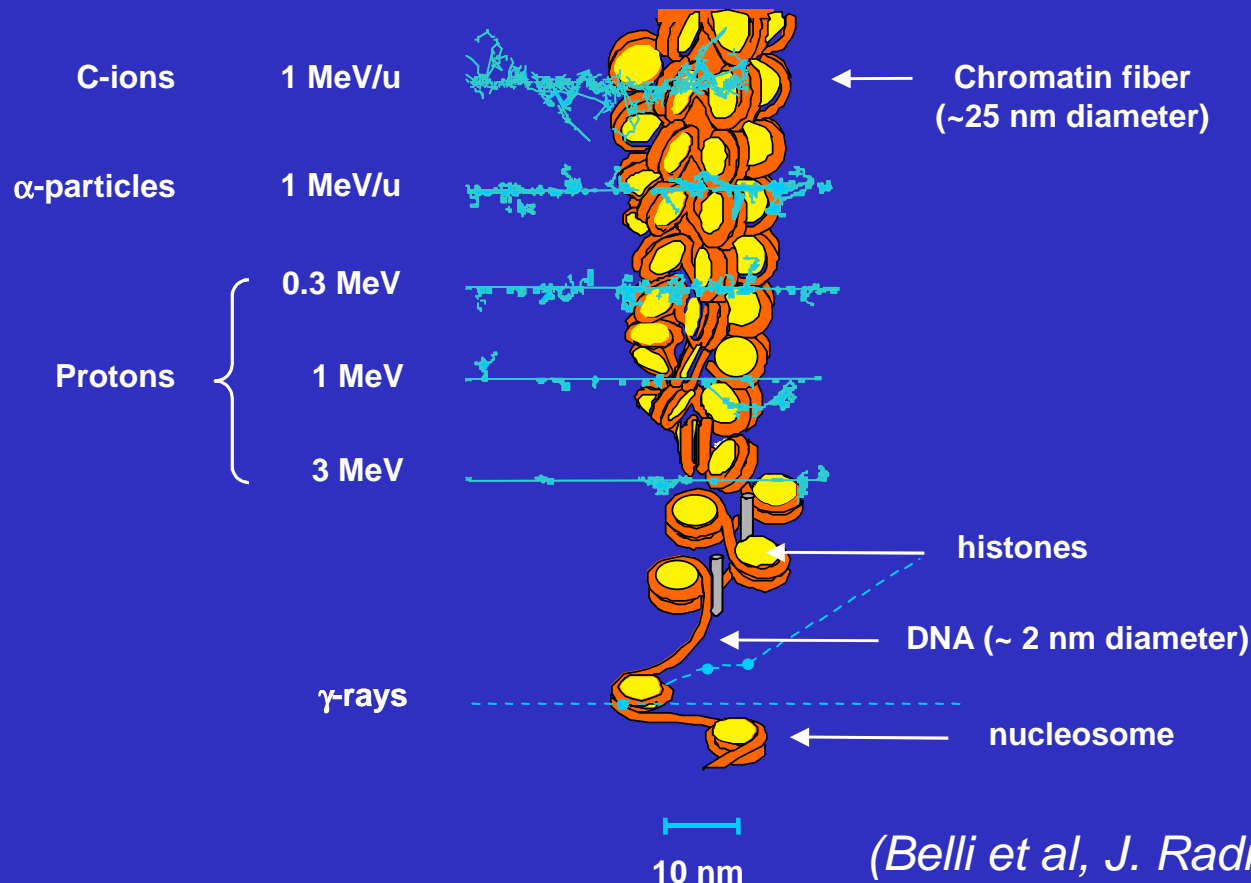
Le **radiazioni fotoniche** interagiscono con la materia biologica prevalentemente per effetto Compton, dando luogo ad elettroni secondari di alta energia, sparsamente ionizzanti, ovvero di basso LET (tranne che a fine percorso).

La qualità della radiazione **non varia sostanzialmente** nell'attraversare i tessuti, cosicché l'effetto biologico è determinato dalla dose assorbita.

Le **particelle cariche** (protoni o ioni più pesanti anche di energia relativamente elevata) perdono energia con interazioni più frequenti con la materia biologica rispetto ai fotoni. In conseguenza del rallentamento il loro LET aumenta. Oltre agli ioni primari vi possono essere particelle secondarie prodotte da interazioni nucleari dei primari con la materia attraversata (queste interazioni possono produrre la frammentazione sia del proiettile che del bersaglio). La qualità della radiazione **varia** durante l'attraversamento dei tessuti. La dose (o la fluenza) non è l'unico parametro che determina l'effetto biologico

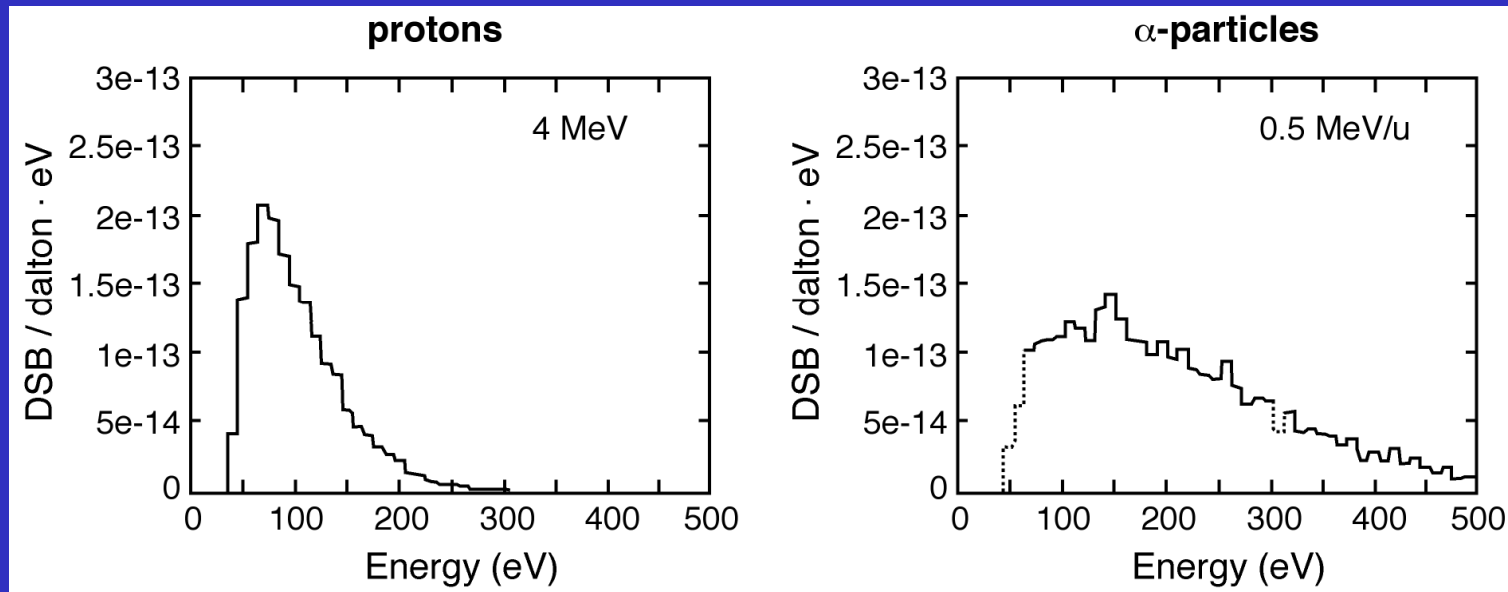
Distribuzione microscopica dell'energia: cluster di ionizzazioni nel bersaglio

INTERPLAY TRACK - CHROMATIN (at the nucleosome/fiber levels)
Clustered DNA damage - Reparability of DNA lesions



(Belli et al, J. Radiat. Res, 2002)

Complexity of DSB



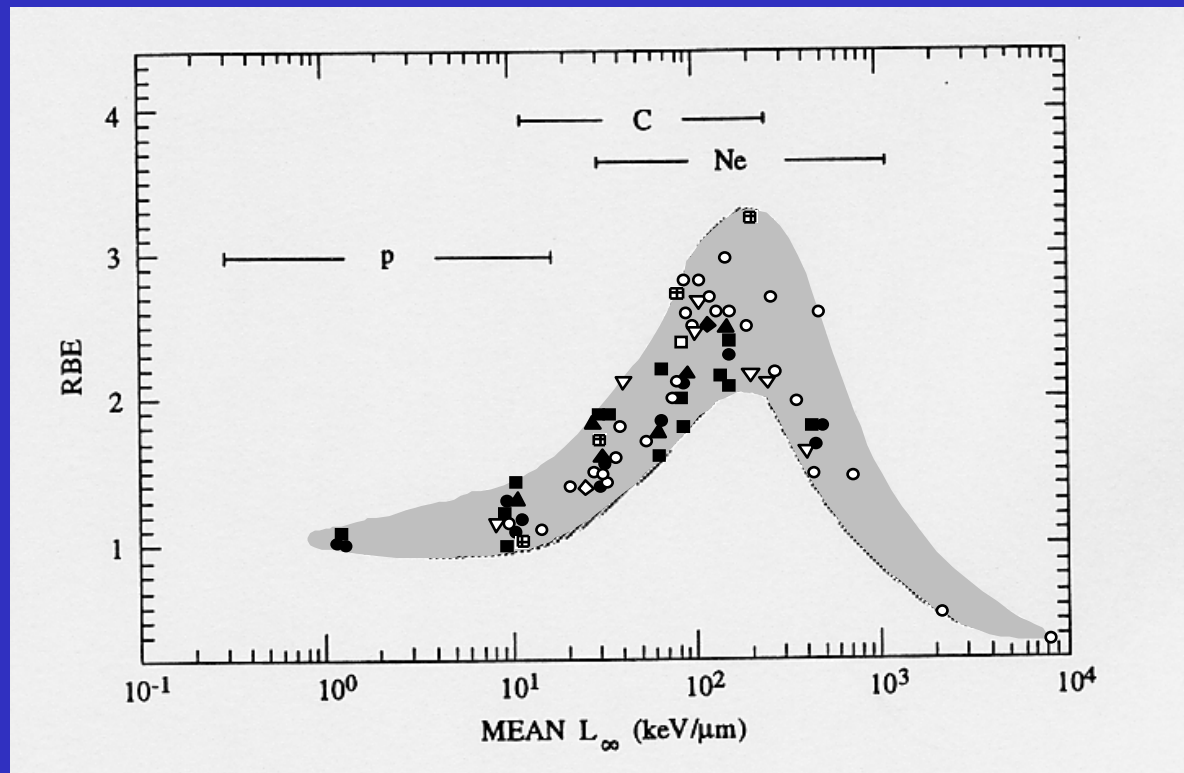
Calculated distribution of energy deposited in DNA segments (30 bp) where a DSB has occurred (adapted from *Ottolenghi and Merzagora 1997*).

Qualità della radiazione e altri aspetti della risposta cellulare

- Effetto ossigeno (radioresistenza di cellule ipossiche)
- Modulazione della radioresistenza/radiosensibilità nelle varie fasi del ciclo cellulare
- Riduzione dell'effetto con dosi frazionate

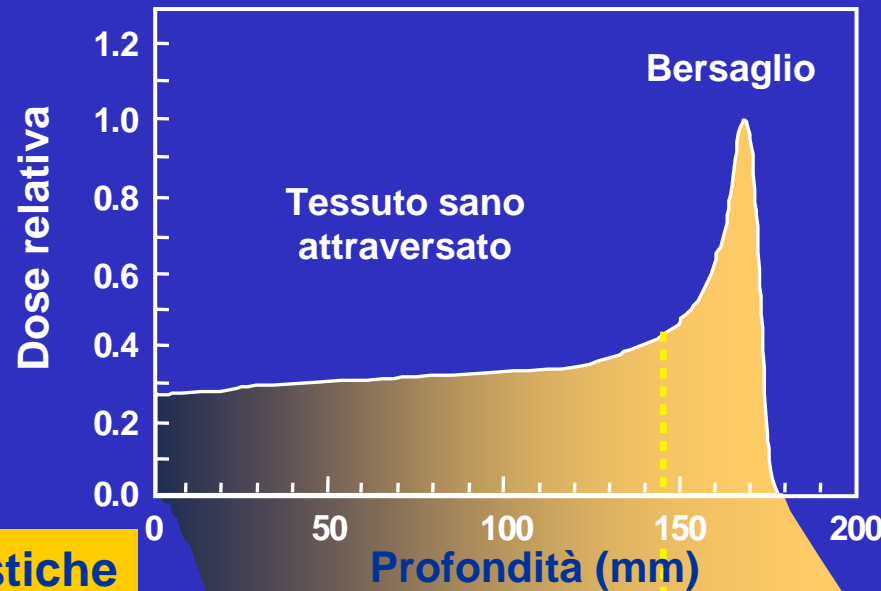
Relazione tra RBE e LET

RBE al 10% di sopravvivenza (*Blakely et al, Heavy ions radiobiology:cellular studies. Adv. Radiat. Biol. 1984*)



Dati da numerose linee cellulari

Potenziati vantaggi dell'adroterapia



Caratteristiche

E	“alta”	“bassa”
LET	“basso”	“alto”
Dose	bassa	elevata
RBE	≈ 1	> 1
OER	≈ 3 (X, γ)	< 3
Dipend. ciclo cell.	elevata	bassa
Dipend. dD/dt	si	scarsa

Potenziati Vantaggi

Elevata D al tumore con risparmio tessuti circostanti

Maggiore letalità nel bersaglio, efficacia per tumori radioresistenti

Minore frequenza di recidive a causa di cellule ipossiche

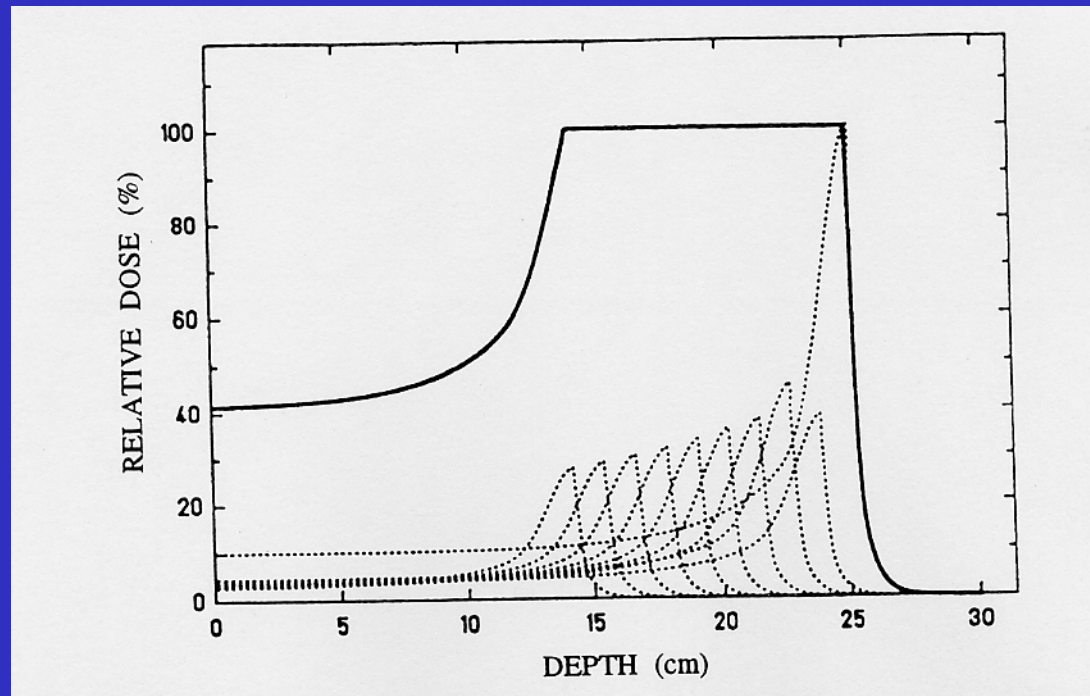
Maggiore letalità nel bersaglio per minor numero di cellule in fase resistente

Possibilità di frazionamento per risparmiare tessuto sano

Ma la realtà è.....

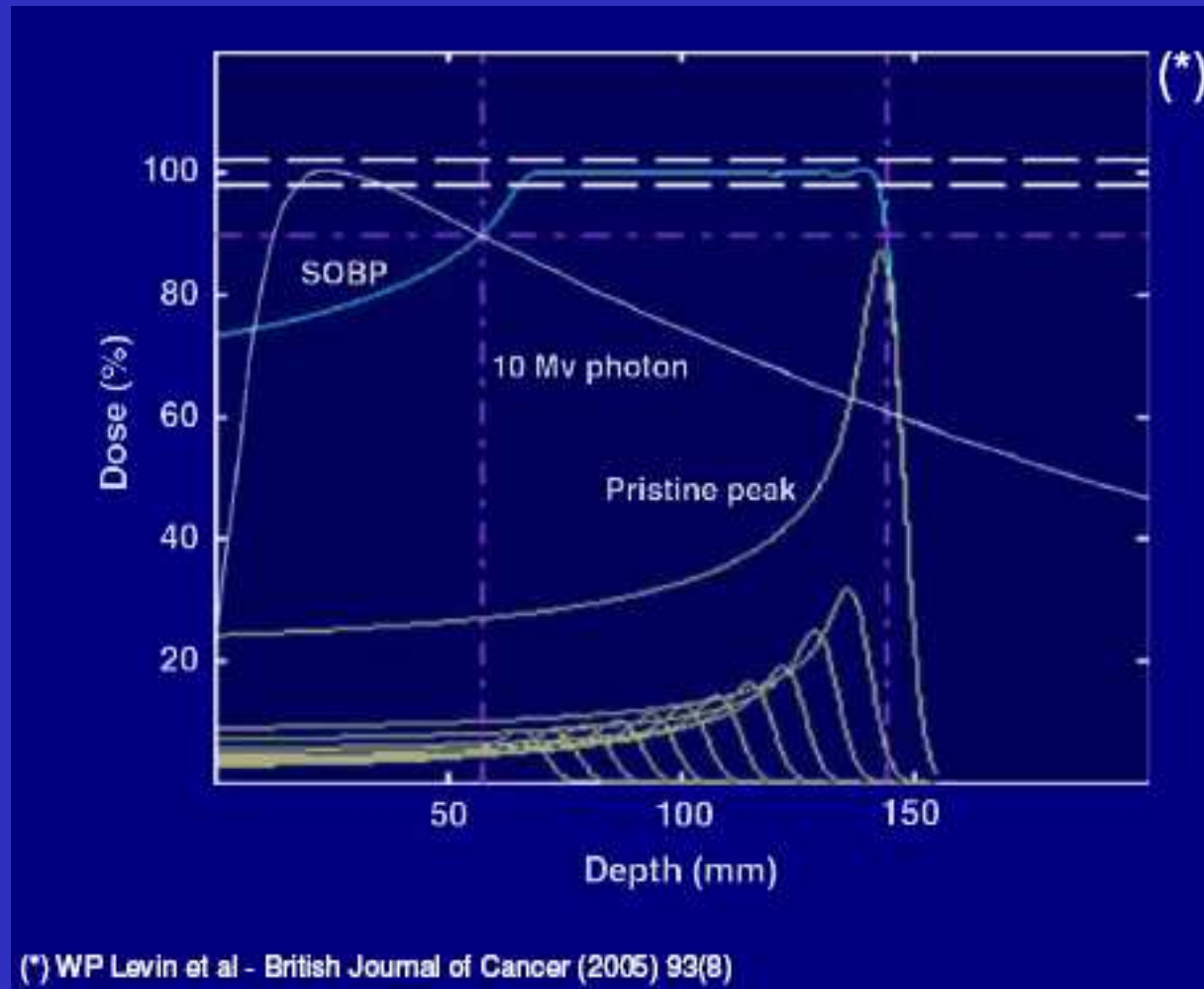
Spread Out Bragg Peak (SOBP)

Picco di Bragg allargato (Spread-Out Bragg Peak = SOBP)



Variando l'energia durante l'irradiazione in modo ben controllato è possibile sovrapporre molti picchi di Bragg ed ottenere un SOBP

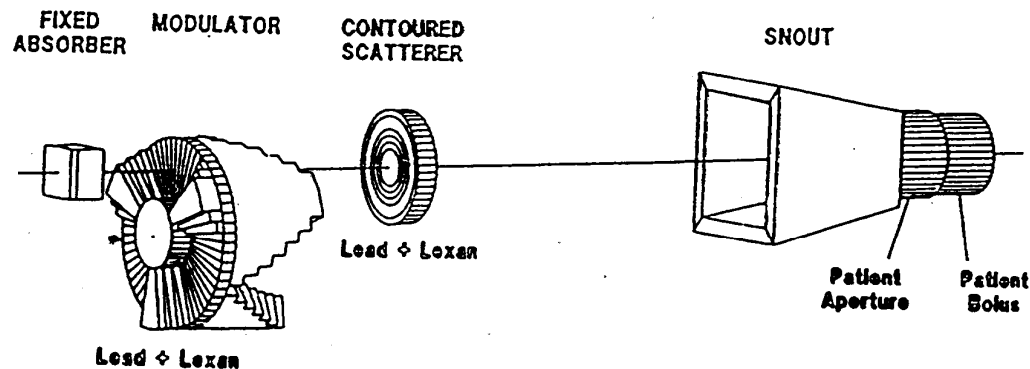
The Spread Out Bragg Peak (SOBP)



Superimposition of Bragg peaks with different energies to cover the tumour volume

La distribuzione della dose

Passive devices



Active devices

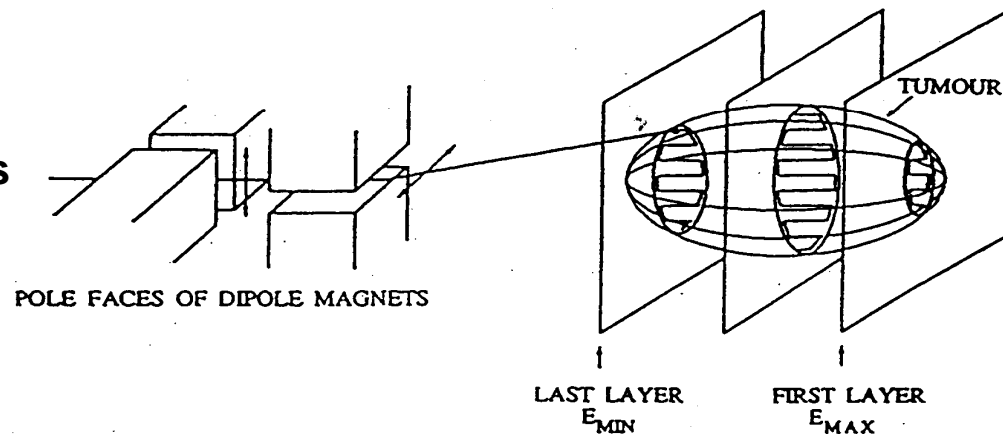
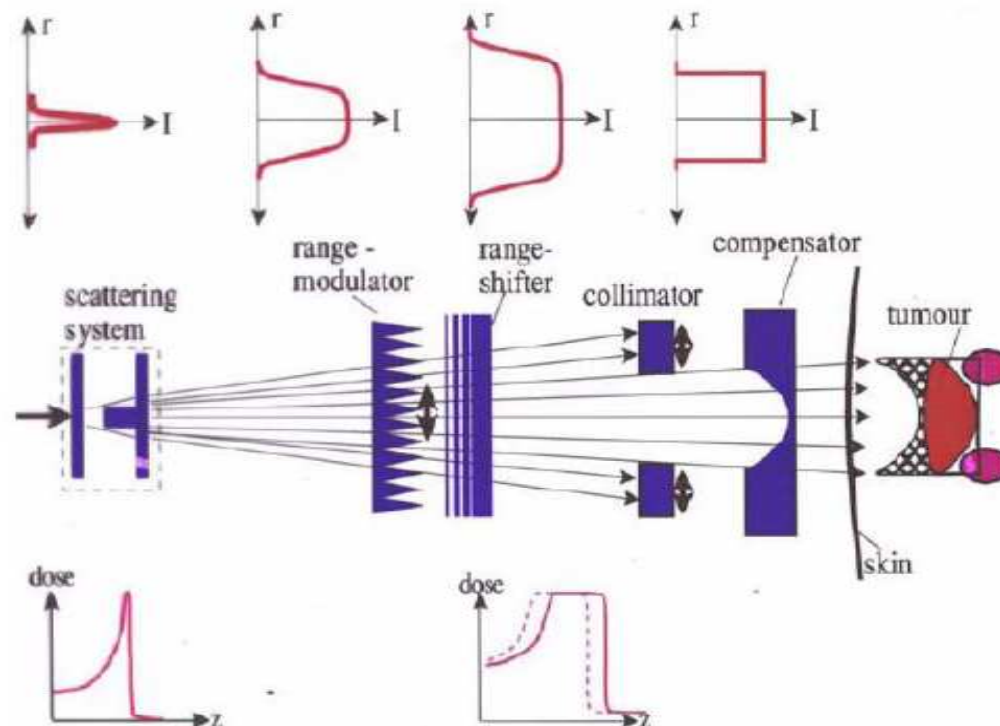


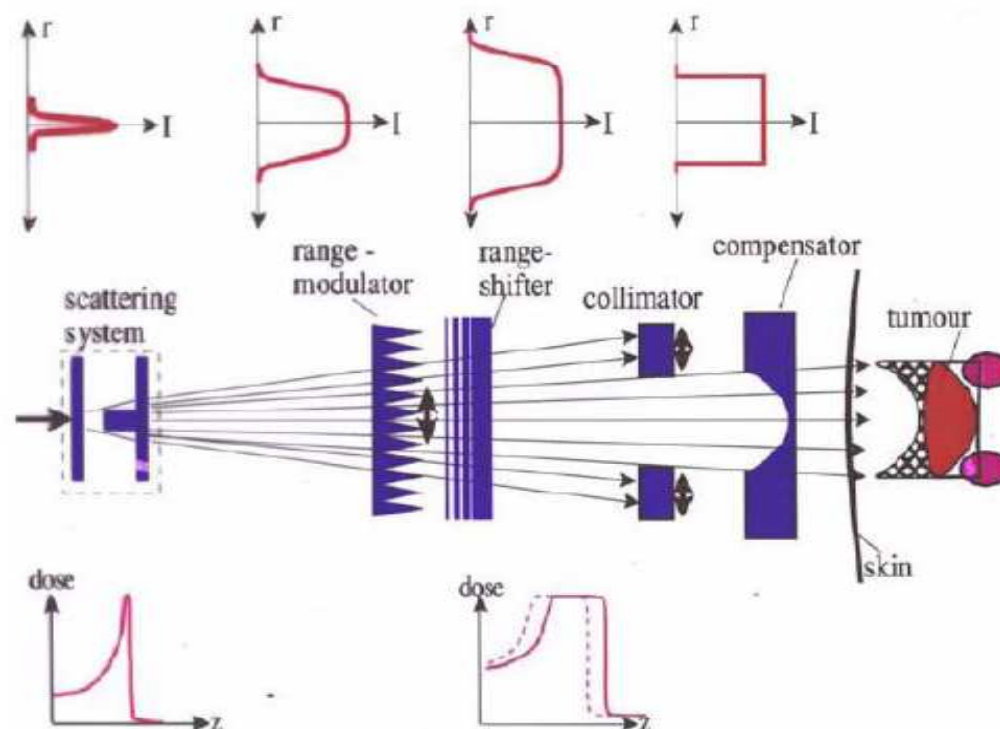
Figura 6. La figura mostra in modo schematico i metodi passivi e attivi di distribuzione della dose. Sino al 1995 soltanto i primi sono stati utilizzati per trattare pazienti. Dal 1996 due sistemi attivi molto sofisticati sono entrati in funzione presso due centri di ricerca in fisica nucleare: il PSI presso Zurigo (protoni) e il GSI presso Darmstadt (ioni carbonio).

La distribuzione della dose: sistemi passivi



- have to be manufactured for each patient field
- fixed extension and extended Bragg peak
- missing proximal conformation

La distribuzione della dose: sistemi passivi



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- fixed extension and extended Bragg peak
- missing proximal conformation

La distribuzione della dose: sistemi passivi

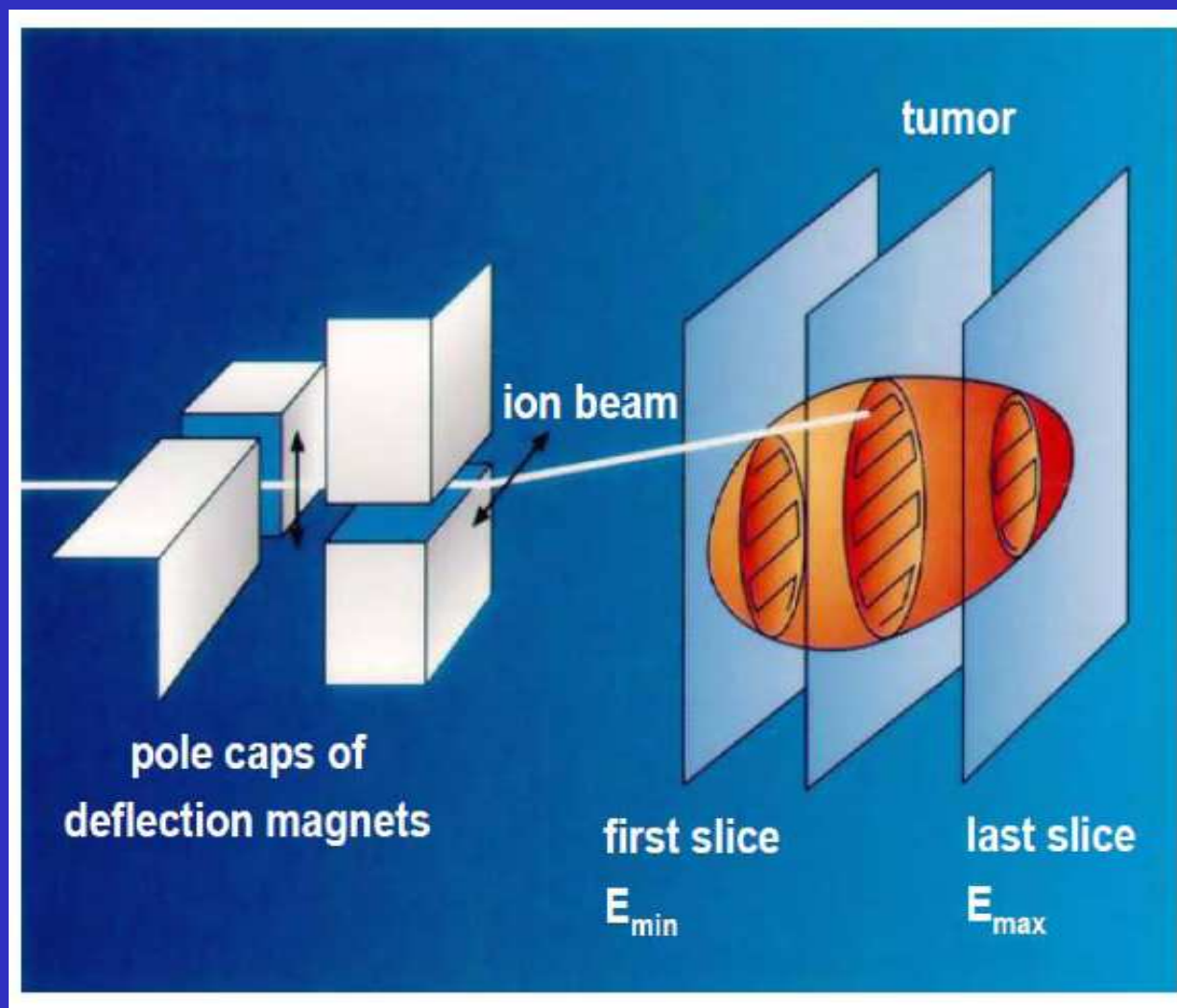


Collimator



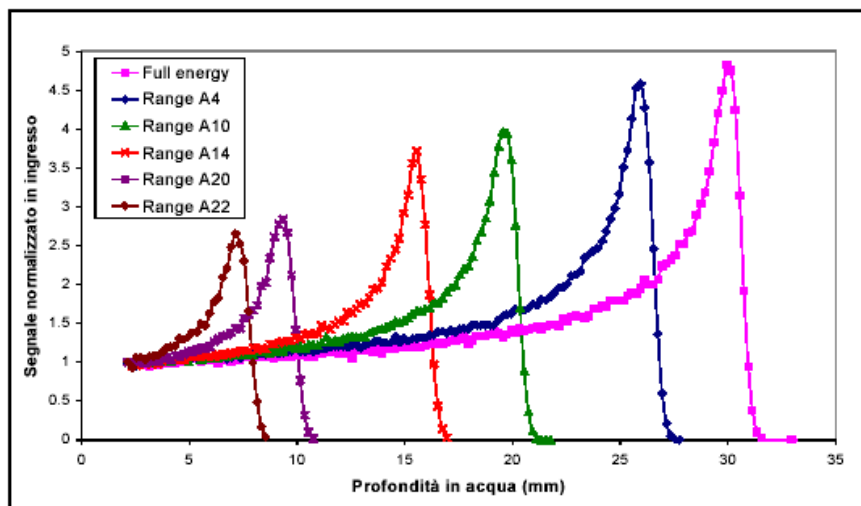
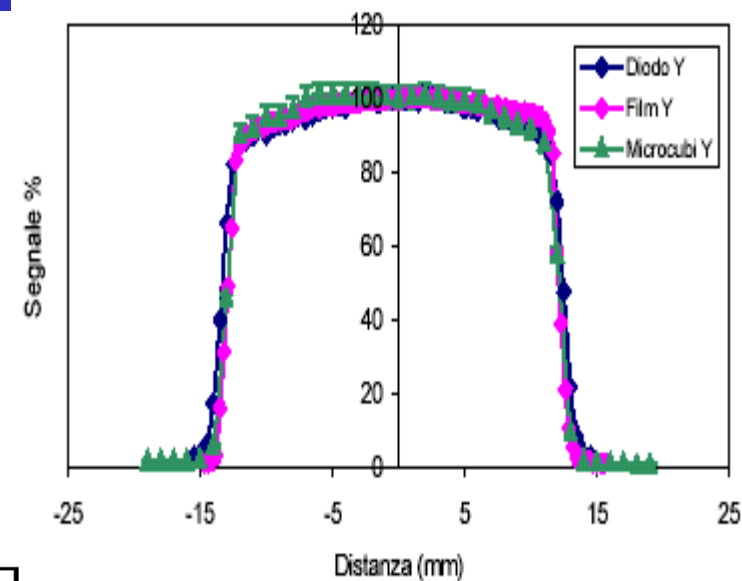
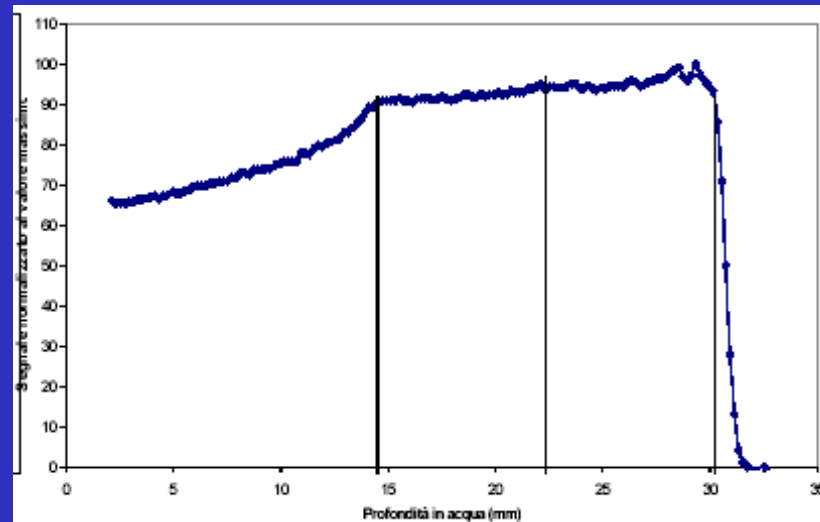
Compensator

La distribuzione della dose: sistemi attivi



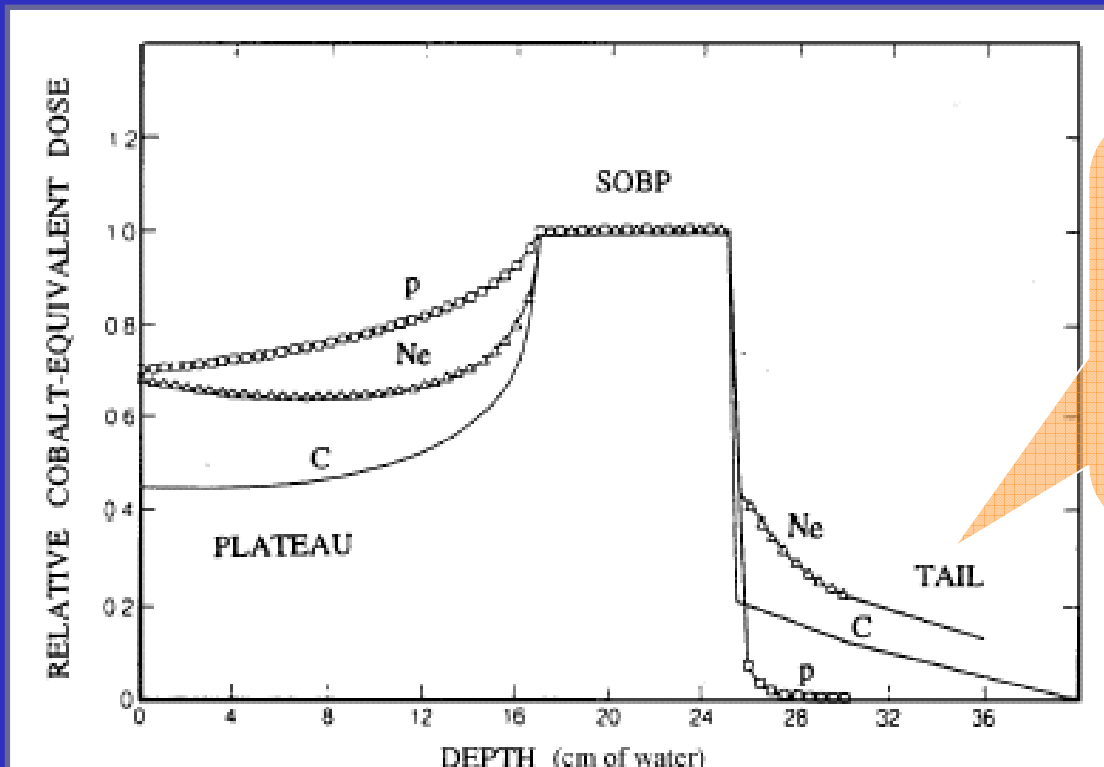
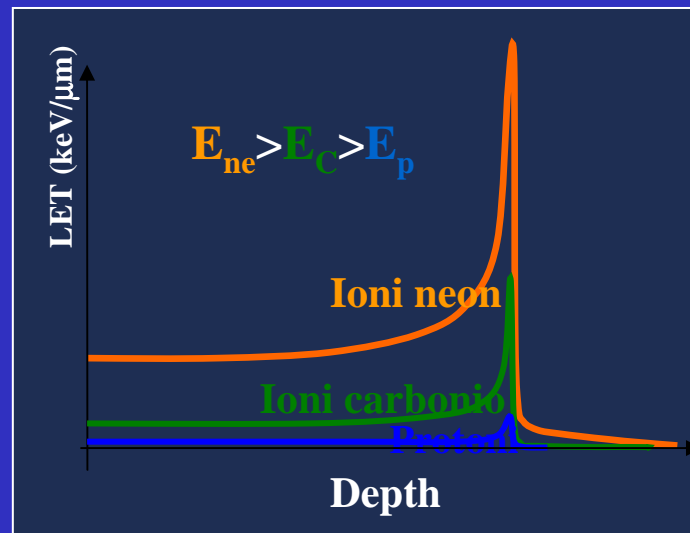
Raster scanning

Profilo fascio protoni CÀTANA



(Cuttone et al 2003)

La curva di Bragg per vari ioni



Dose beyond the Bragg peak:

p ~ 1-2 %

C ~ 15 %

Ne ~ 30 %

Tradurre in pratica i potenziali vantaggi

Per tradurre i vantaggi **fisici/dosimetrici** e **biofisici/radiobiologici** in vantaggi **clinici** è necessaria l' **ottimizzazione** dei piani di trattamento.

Ciò implica:

- una opportuna **dosimetria** del fascio terapeutico;
- una buona conoscenza delle proprietà **radiobiologiche** delle particelle

Basi biofisiche e radiobiologiche dell'adroterapia

Le proprietà radiobiologiche degli adroni sono determinate dalla loro energia

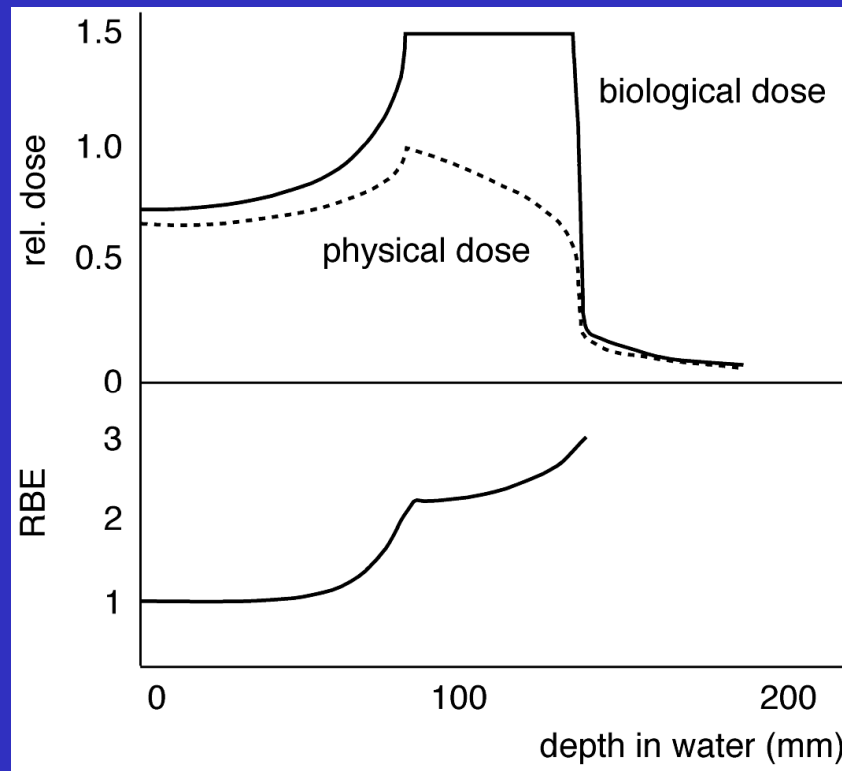
I maggiori valori di dose sono raggiunti in profondità in corrispondenza del picco di Bragg ove prevalgono adroni di bassa energia.

L'RBE dei protoni aumenta significativamente nella zona distale (fall-off) dello SOBP.

L'RBE di ioni più pesanti aumenta lungo l'intero SOBP ed in alcuni casi si produce una “coda” di dose dovuta a particelle secondarie anche dopo il fall-off.

Necessaria la conoscenza dettagliata della
dipendenza dell'RBE dall'energia (o dal LET) degli adroni
(per i protoni sono rilevanti solo le basse energie ($< \approx \text{MeV}$)).

Physical and biological doses



To obtain a homogeneous biological effect over the tumour volume the physical dose has to decrease towards the distal edge of the SOBP to take into account the **RBE variations**

Obiettivi dei piani di trattamento (TP) in adroterapia

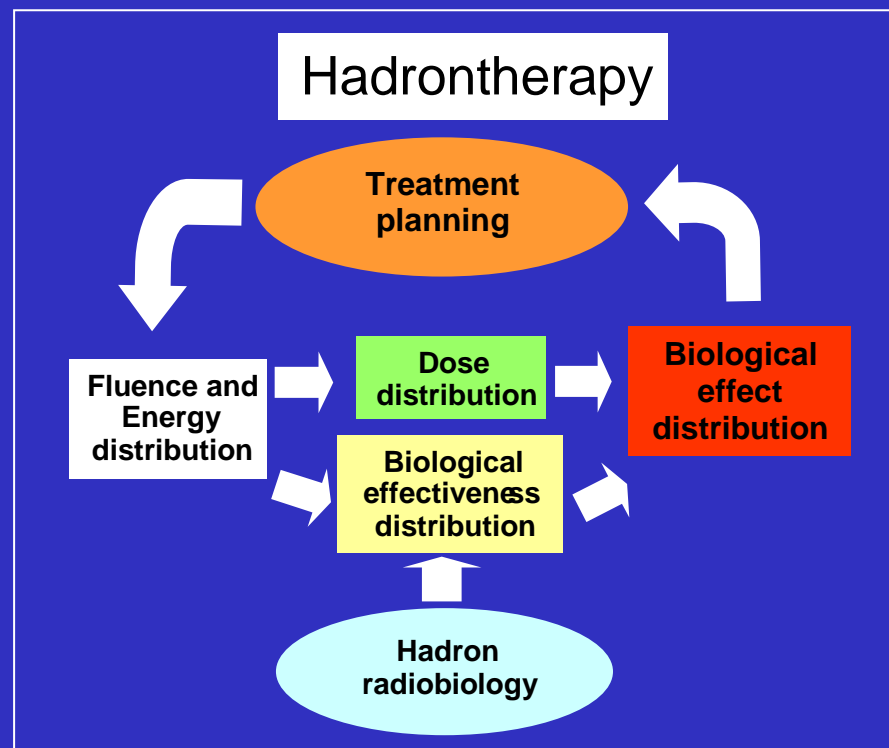
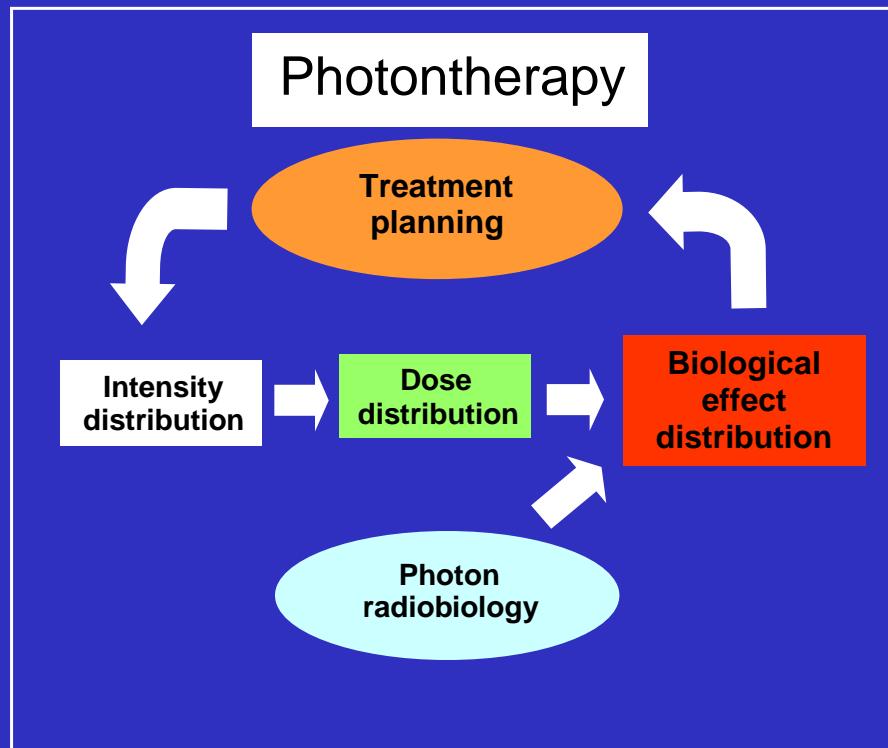
Obiettivo radioterapia :

effetto biologico desiderato = sterilizzazione del tumore (morte cellulare) con il minimo danno al tessuto sano

Metodo ottimale:

formulazione dei **piani di trattamento** non solo con **superfici isodose**,
ma con **superfici isoeffetto**

Treatment planning optimization in hadrontherapy



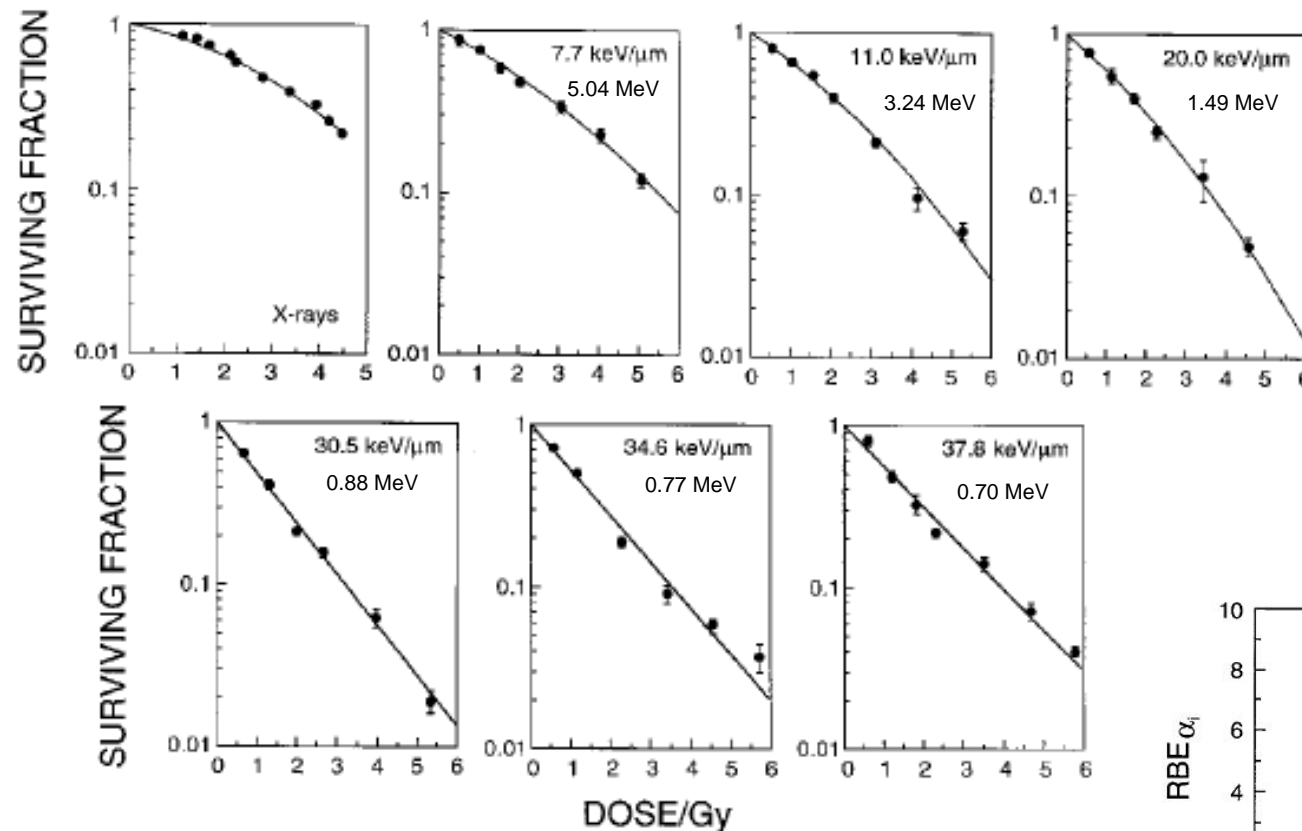
Finding the clinical RBE: the mixed field challenge

- 1. Empirical data based on clinical experience**
- 2. Models able to predict the effects in mixed fields**

Most of the present knowledge on charged particle radiobiology comes from in vitro studies

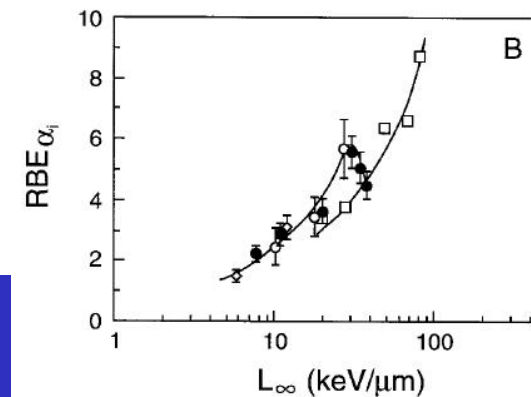
- **Pioneering studies in Berkeley-USA and other Labs.**
- **Great deal of work at hadrontherapy Centres in operation, both for protons (Boston-USA, Loma Linda-USA, PSI-Switzerland, ...) and C-ions (HIMAC-Japan, HIBMC-Japan, GSI-Germany)**
- **...but for low energy protons: studies with accelerators at research facilities (Milan University-Italy, INFN-LNL-Italy, Gray Laboratory-UK, Naples University-Italy)**

Cell inactivation by monoenergetic protons (LNL)



V79 chinese
hamster (rodent)
cells

RBE maximum
at ~ 40 keV/μm



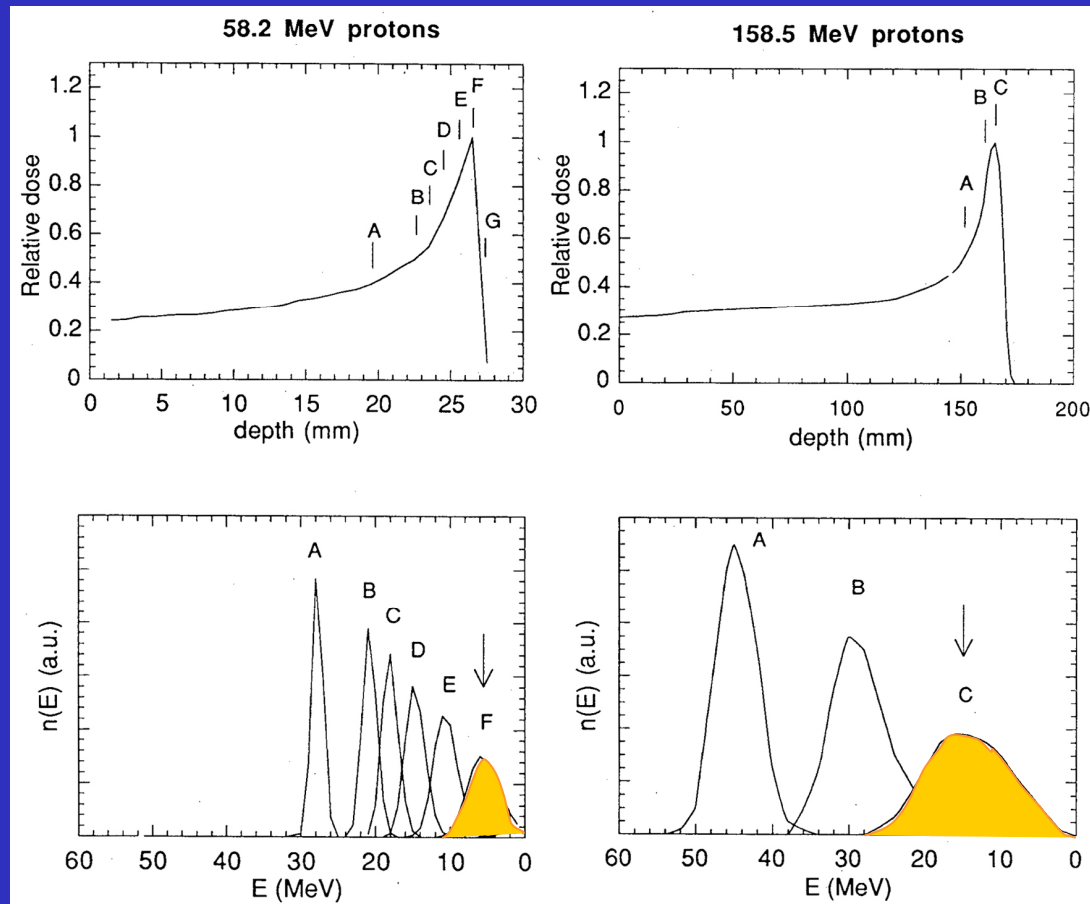
From: *Belli et al IJRB, 1998.*

RBE in SOBP for proton beams

RBE increases at the SOBP **distal region**:

- Robertson et al (1975) observed an extension of about 2 mm in the “biological” SOBP of 160 MeV protons, due to RBE increase at the distal part
- Courdi et al (1994) and Bettega et al (2000) observed an RBE increase up to 1.2-1.3 in the distal part of the SOBP of a ~ 60 MeV proton beam

Understanding why radiation quality in a proton Bragg peak depends on initial energy

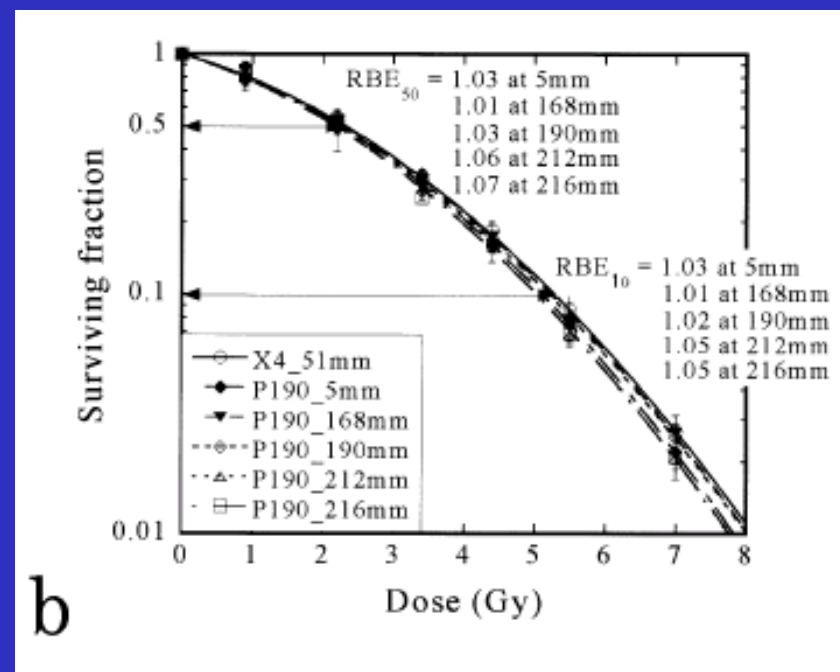
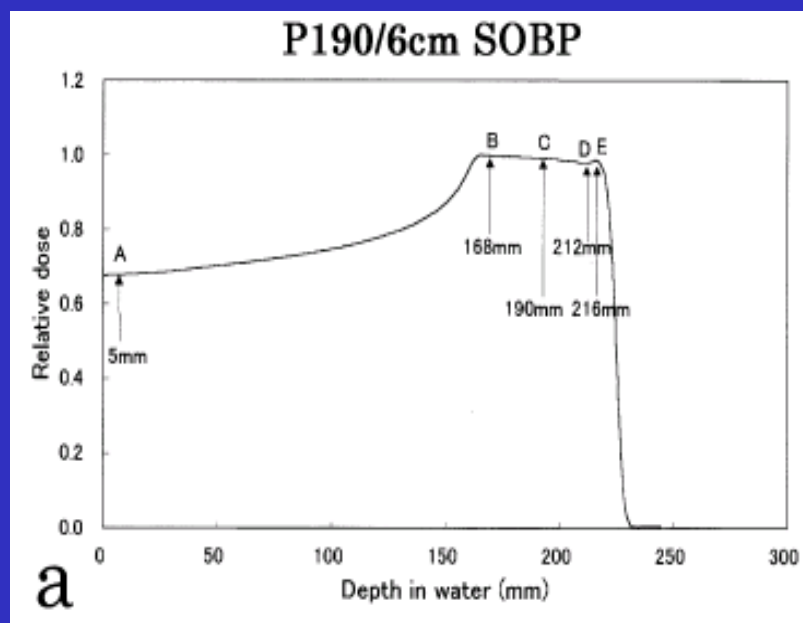


Simulation
with a MC
code

The proportion of low-energy, high-LET, protons varies with depth and **depends on the initial beam energy**

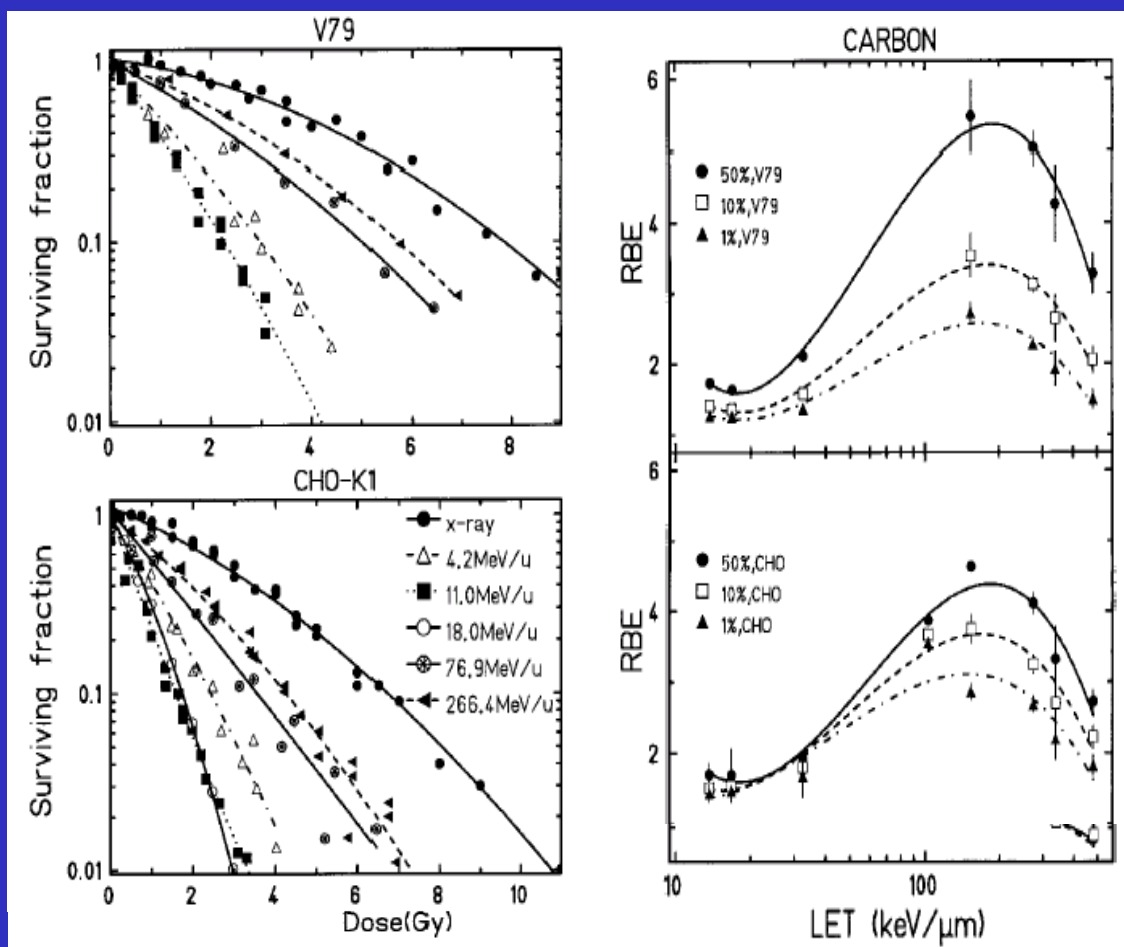
RBE of protons does not change much along the SOBP

- 6 cm SOBP generated by 190 MeV proton beam at Hyogo
 - Human Salivary Gland (HSG) cells
 - RBE = 1.03 – 1.05 (except at the distal part)



From: *Kagawa et al. Preclinical biological assessment of proton and carbon ion beams at Hyogo Ion Beam Medical Center . Int.J.Rad.Onc.Bio.Phys.,2002*

Cell inactivation by monoenergetic C ions (GSI)



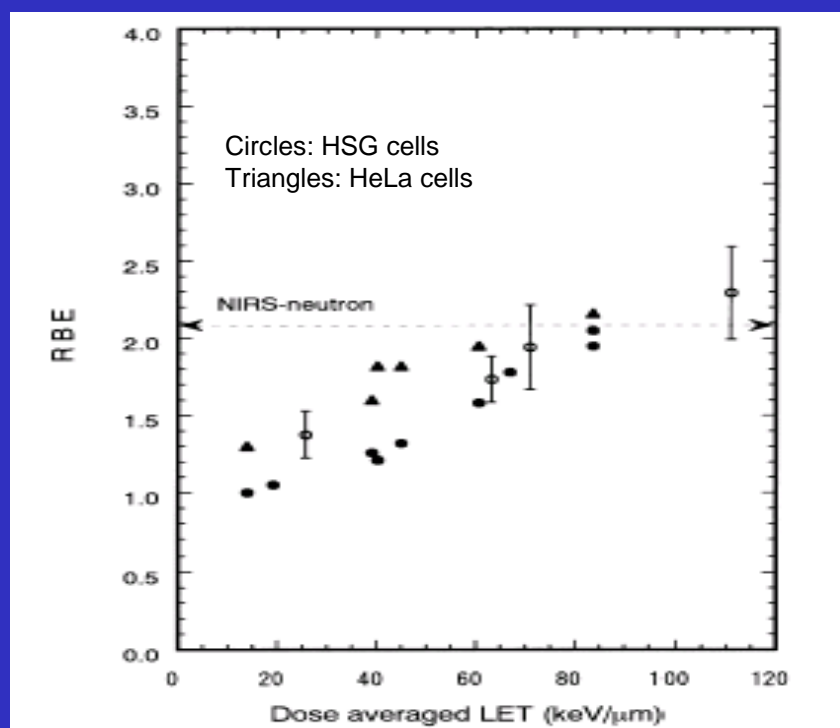
C. hamster (rodent) cells

RBE maximum
at 150 – 200 keV/μm

From: *Weyrather et al 1999. RBE for carbon track-segment irradiation in cell lines of differing repair capacity.*

RBE of C ions changes along the SOBP

RBE at different positions in the 6 cm SOBP generated by a 290 MeV/u C beam at HIMAC



Depth-dose curves for a 6 cm SOBP generated by 290 MeV/u C beam at HIMAC: “physical” and “biological” doses

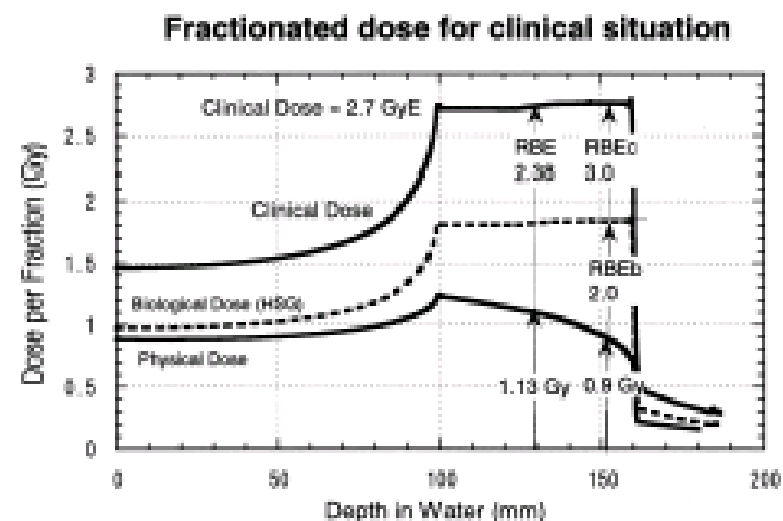


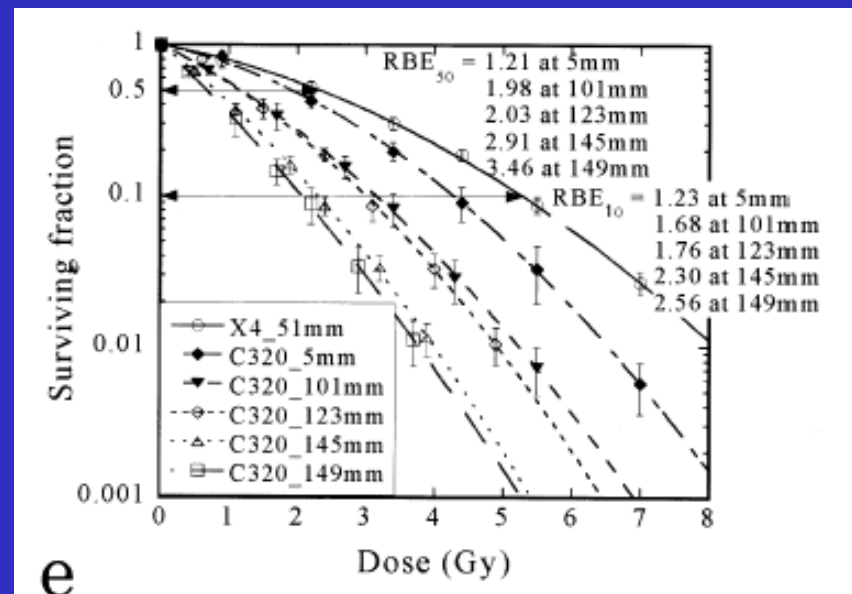
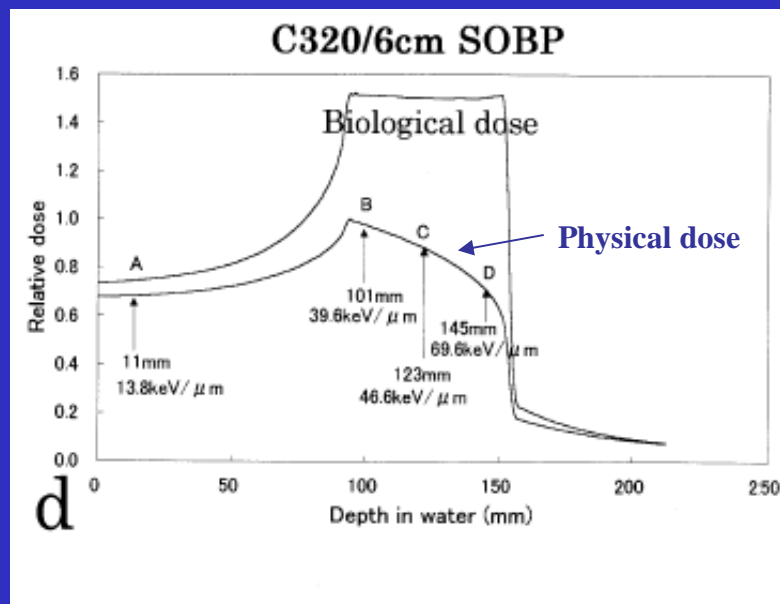
Fig. 5. Schematic method used to determine the RBE at the center of the SOBP for the clinical situation.

From: *Kanai et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int.J.Rad.Onc.Biol.Phys., 1999*

RBE of C ions changes along the SOBP

Depth-dose curves for a 6 cm SOBP generated by 320 MeV/u C beam at Hyogo: “physical” and “biological” doses

- Human Salivary Gland (HSG) cells
- cell survival and RBE at different positions in the 6 cm SOBP



From: *Kagawa et al. Preclinical biological assessment of proton and carbon ion beams at Hyogo Ion Beam Medical Center . Int.J.Rad.Onc.Biol.Phys.,2002*

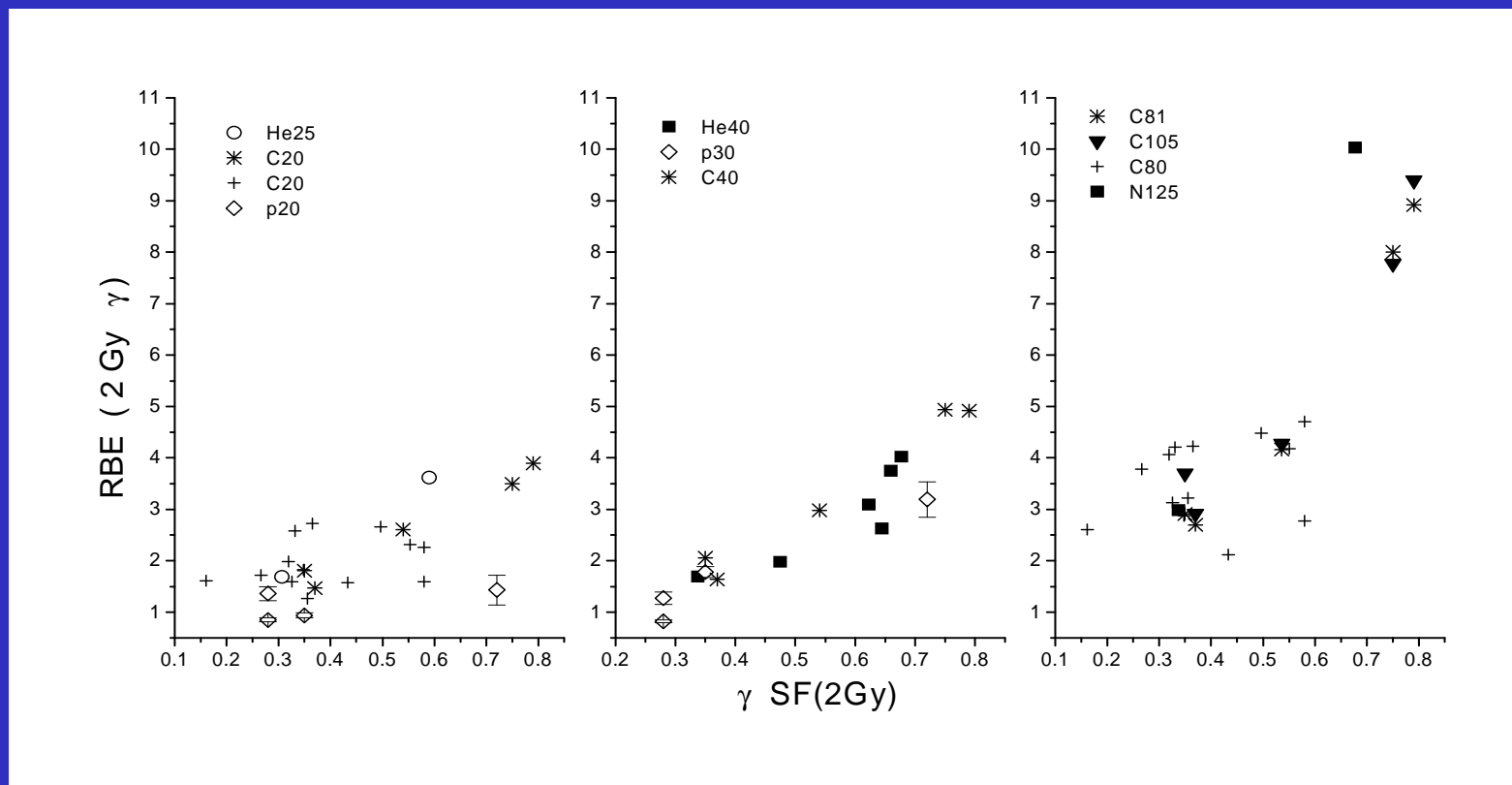
RBE of C ions and repair capability

Some facts suggest that RBE for carbon ions correlates with cell repair ability:

- In L5178Y S/S cells there is a pronounced RBE maximum only when repair is permitted (Lett et al. 1989)
- In AT cells, deficient in damage recognition, there is an RBE maximum smaller than in repair-proficient T1 cells (Lavin and Shiloh, 1997)
- In glioblastoma cells with p23 mutation (less sensitive to X-ray induced apoptosis) RBE is higher than in wild type cells (Tsuboi et al 1998).
- In CHO-xrs5 hamster cells, deficient for repair, the RBE does not show a maximum and decreases with LET (Weytather et al IJRB 1999)

RBE may be higher in cells more resistant to γ -rays

RBE at the survival level given by 2 Gy of γ -rays for cell lines of various radiosensitivity

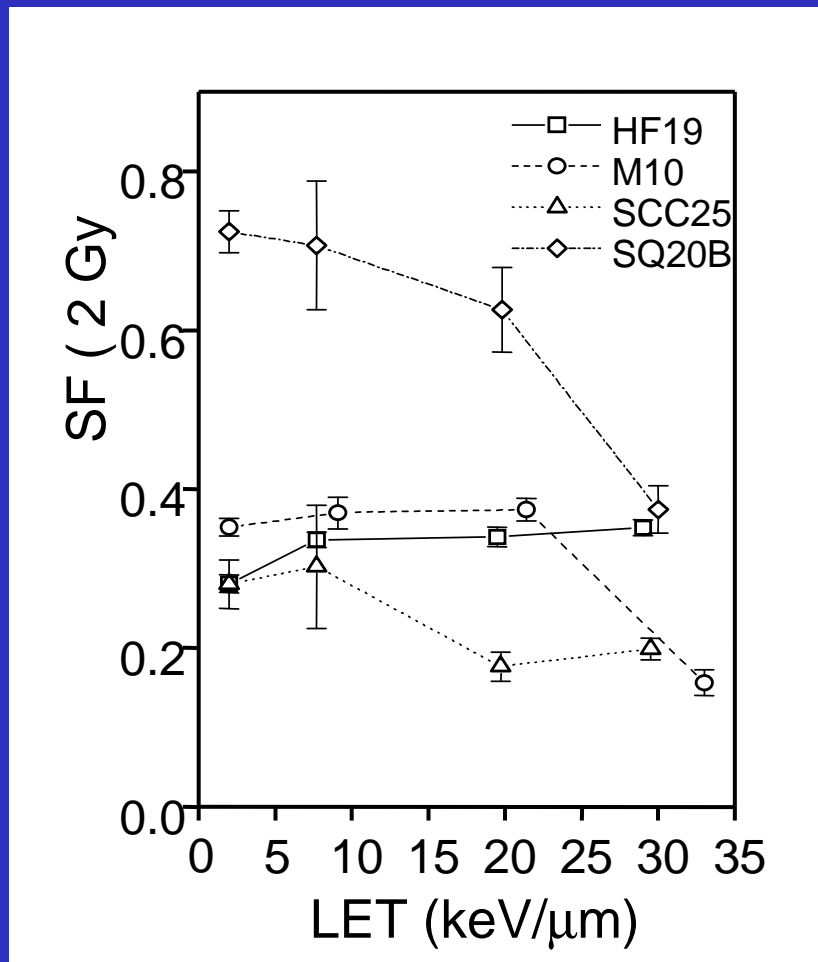


Literature data reviewed in: *Belli et al., Inactivation of human normal and tumour cells irradiated with low energy protons. Int.J.Rad.Biol.,2000*

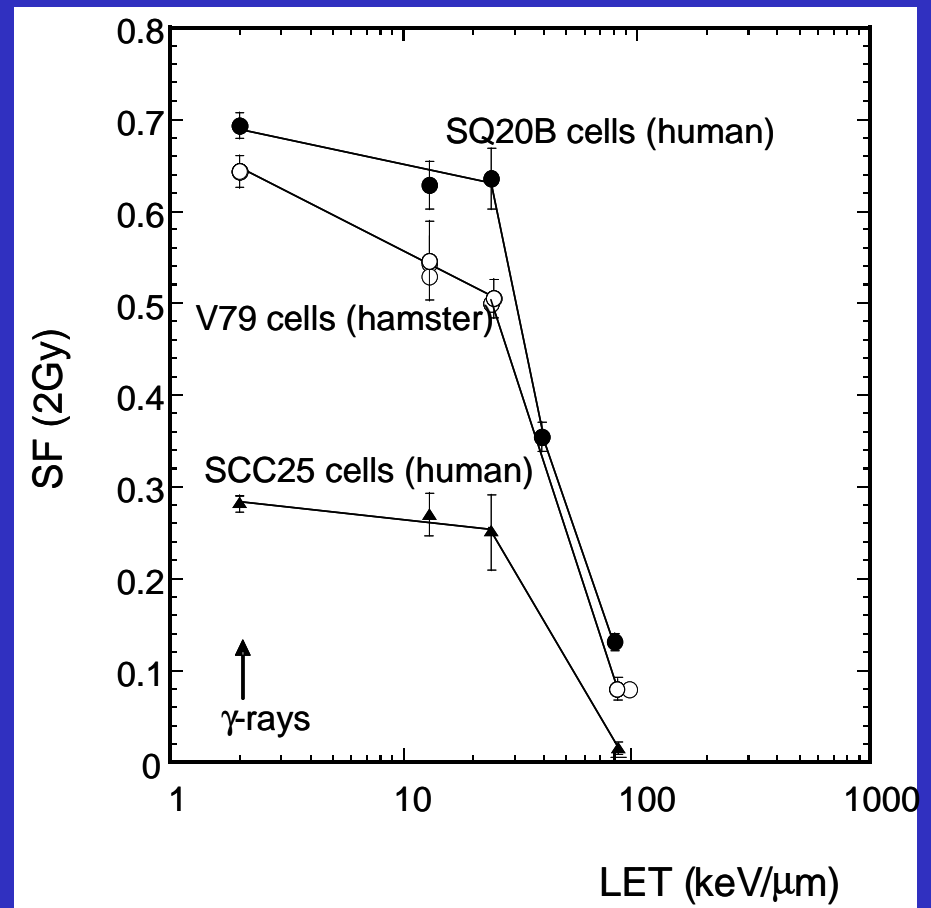
M.Belli – Radiobiologia - UniCa–Sc.Sp.Fis.Med 2011

Radioresistant cells to γ -rays (high SF(2 Gy)) give a large response variation with LET

SF (2Gy) versus LET for monoenergetic protons (*Belli et al., Int.J.Rad.Biol.,2000*)



SF (2Gy) versus LET for monoenergetic C ions (*Belli et al., unpublished results and Bettega, private communication*)



Radioresistant cells that give a large response variation with LET are suitable for radiobiological characterization of a therapeutic beam

For example, radioresistant, repair proficient, Chinese hamster cells are ideal to detect variations in radiation quality in a therapeutic beam with good spatial resolution,

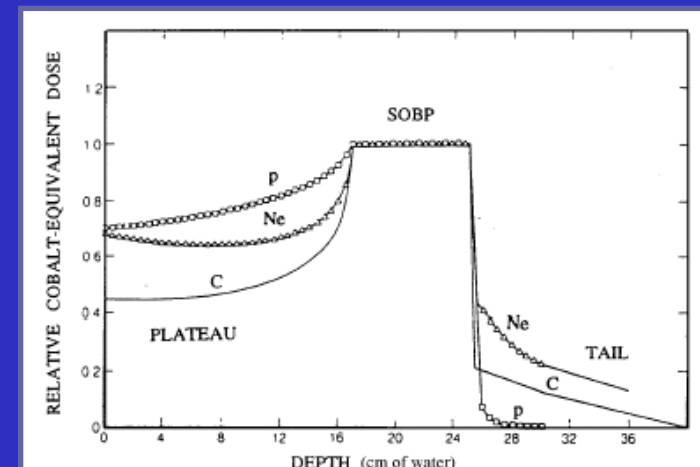
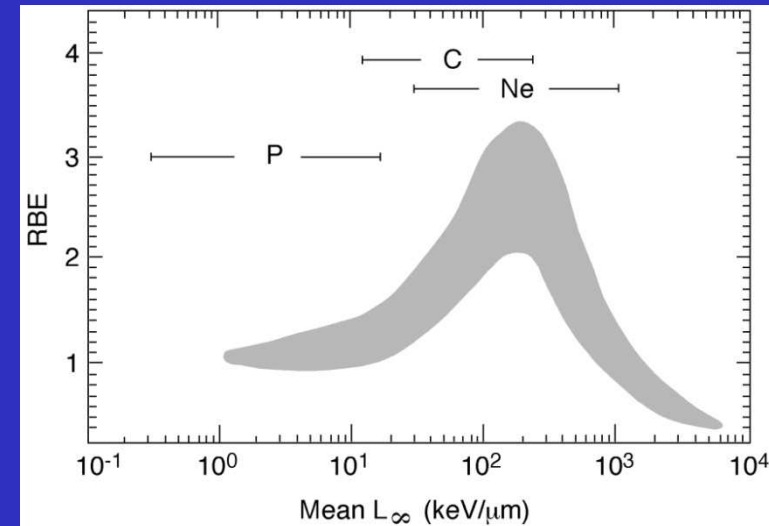
...but nothing to do with clinical RBE !

Rationale for using carbon ions

The LET in a SOBP used to treat deep-seated tumours usually covers the range 40-90 keV/μm. This range is still before the maximum of the RBE-LET relationship, therefore avoiding the “overkilling” region (where energy is “wasted”).

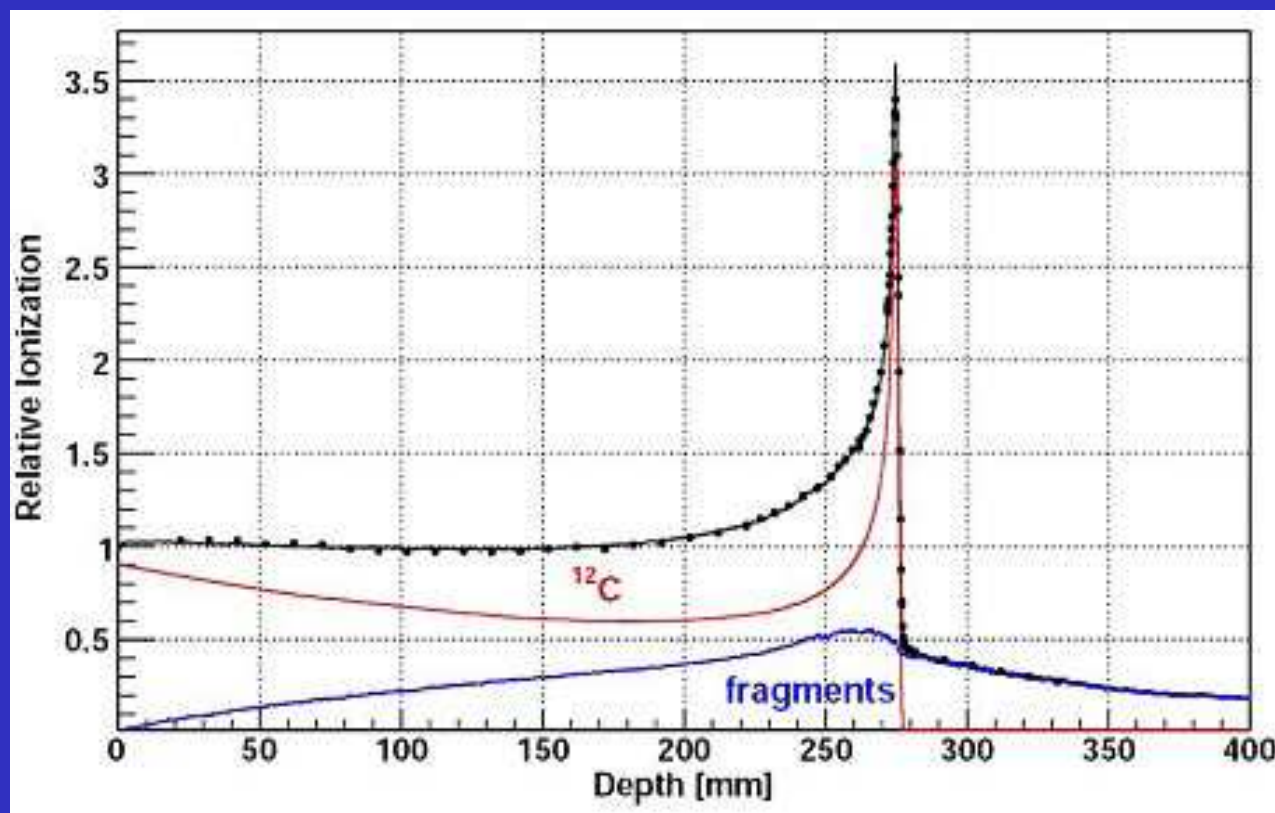
Ions heavier than C have a less steep drop-off at the SOBP end due to light fragments produced by nuclear reactions.

C ions are considered the “best choice” among ions heavier than protons



Carbon ions fragmentation

Rapisarda et al, Il Nuovo Cimento, 2011



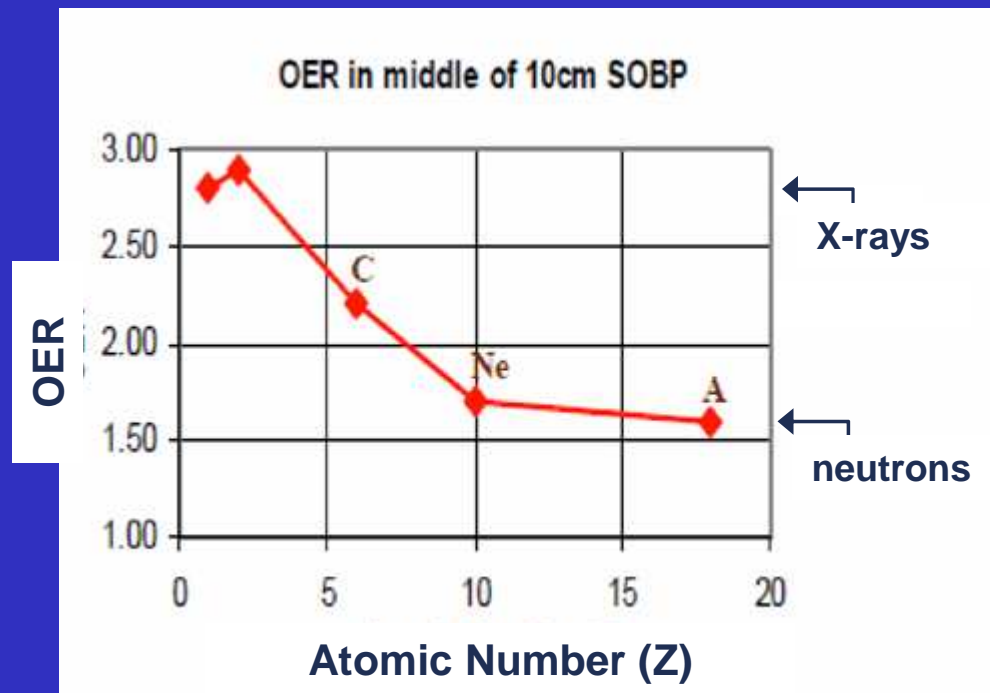
Monte Carlo simulation of the ionization induced by ^{12}C ions in water with (black line) and without (red line) activating nuclear reactions. The blue line represents the produced fragments ionization's contribution. Dots are experimental data.

The “best” heavy ion

- ^{12}C has an intermediate LET so far as biological effects are concerned

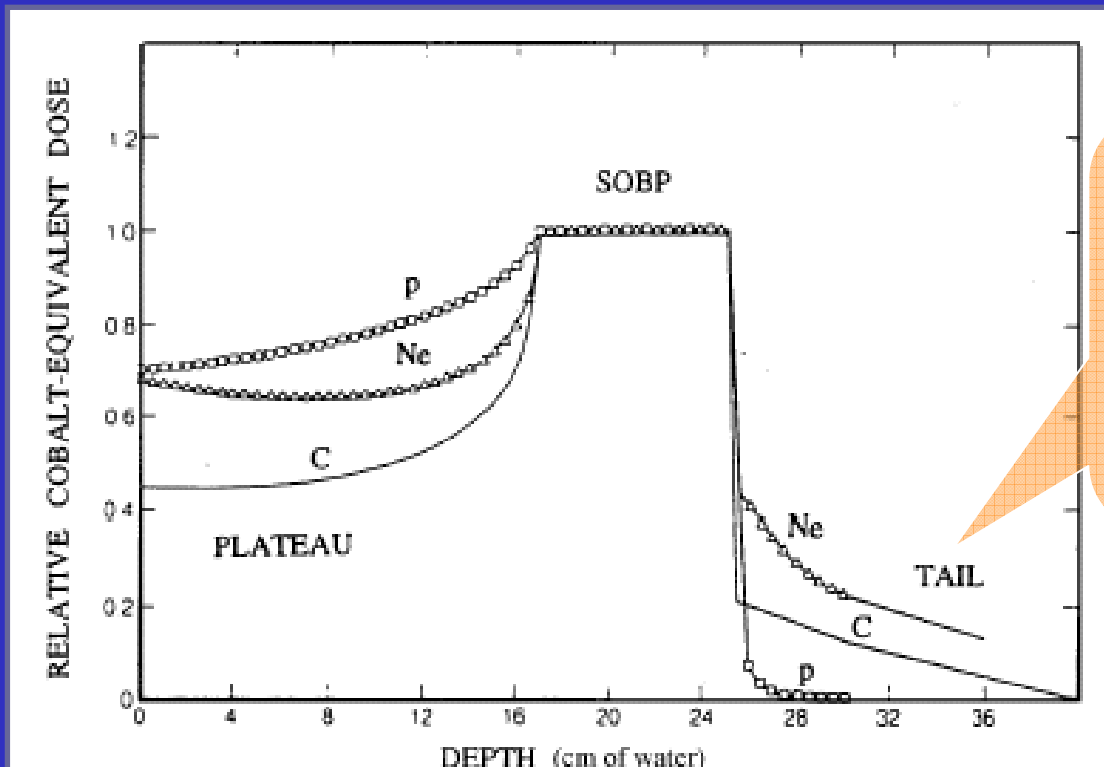
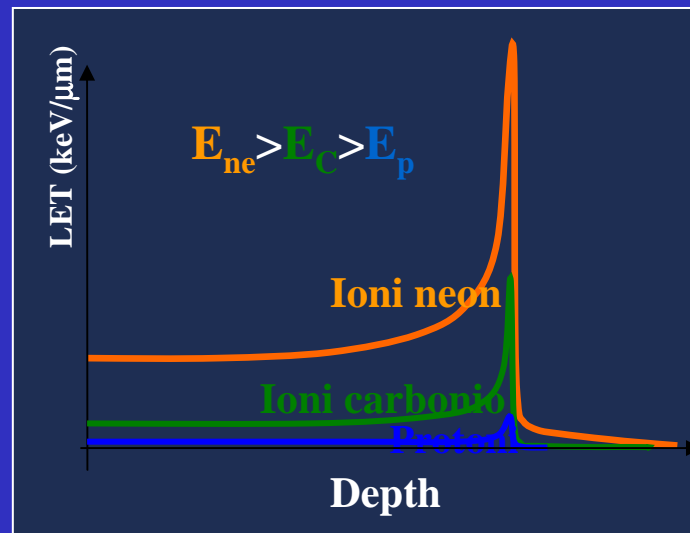
- If one really believes that high LET is an advantage, one should go higher in atomic number

at least up to
 ^{20}Ne ($Z=10$)



Raju *et al.*, IJORBP 51:712-719, 1978

The dose tail



Dose beyond the Bragg peak:

p ~ 1-2 %

C ~ 15 %

Ne ~ 30 %

Protons and carbon ions compared

- For **proton** beams the LET increase is significant only at the **very distal part of the SOBP**
- For **carbon** ions there is a significant LET (and RBE) increase **over all the SOBP** → biological dose \neq physical dose

Some approaches for evaluation of proton RBE in a mixed field

- Microdosimetry (y distributions) Paganetti et al. 1995

- Track structure description

radial profile

Scholz and Kraft 1994

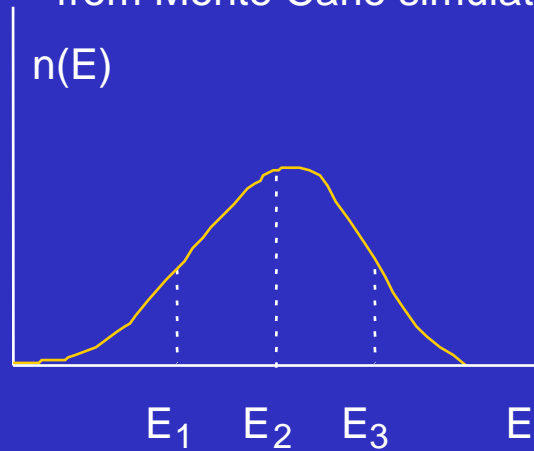
3-D simulation

Ottolenghi et al. 1995

- Semi-empirical (energy distribution) Belli et al. 1995

The semi-empirical approach

Energy spectrum in a specified point
from Monte Carlo simulations



(Belli, Campa, Ermolli, Radiat. Res. 1997)

THE METHOD

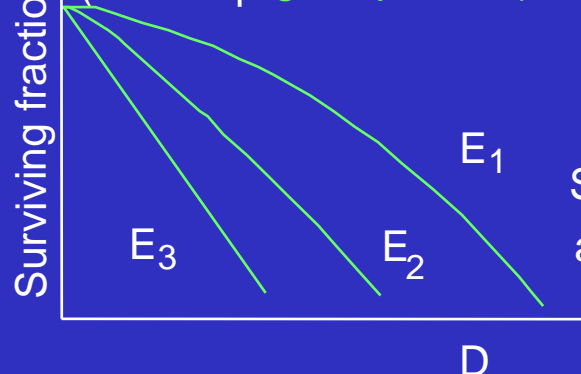
Combining two kinds of information:

- 1) the calculation of the energy distribution of the particles at any given depth by Montecarlo codes
- 2) the experimental knowledge of the dependence of RBE on proton energy

model for interaction of
different components

survival for
the overall
spectrum

Dose-responses for any
energy
(from experiments with
monoenergetic protons)



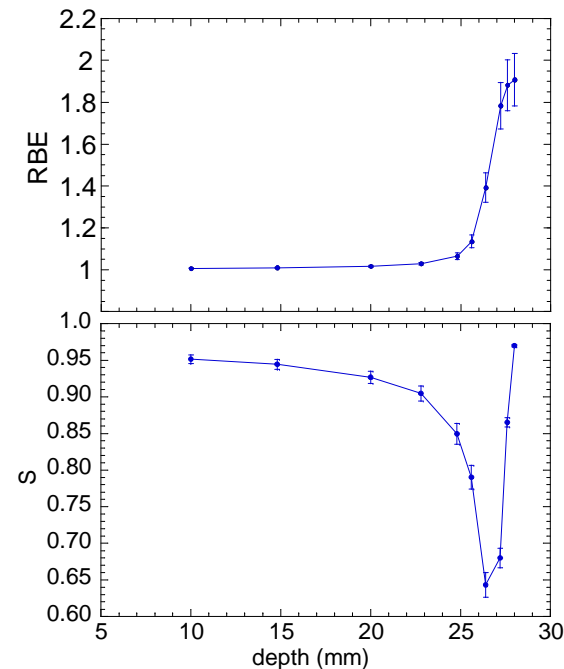
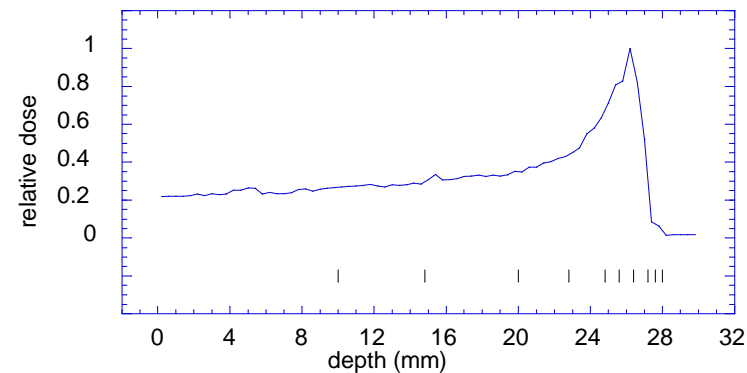
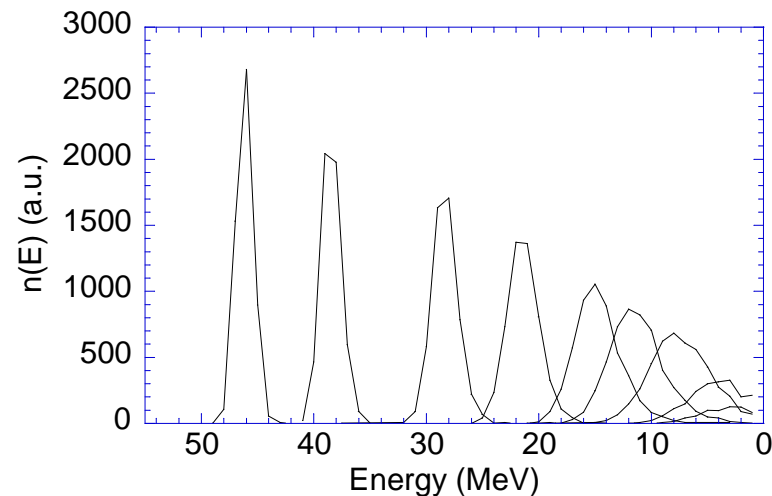
$$S(D, E) = \exp\{-a(E)D - b(E)D^2\}$$

$a(E)$, $b(E)$

The semi-empirical approach

An example:

Results for the unmodulated
proton broad beam for ocular
treatment at PSI
57.7 MeV protons on PMMA



The “3D track structure / complex lesions” model

Ottolenghi, Merzagora, and Paretzke, Radiation Environmental Biophysics 1997,

does not use directly experimental radiobiological data, but they are derived from the physical characteristic of the radiation field assuming a specified mechanism for the occurrence of the relevant biological effects.



complex lesions (two or more dsb within 30 bp) in the cellular DNA as a consequence of ionization clusters produced by the radiation fields.

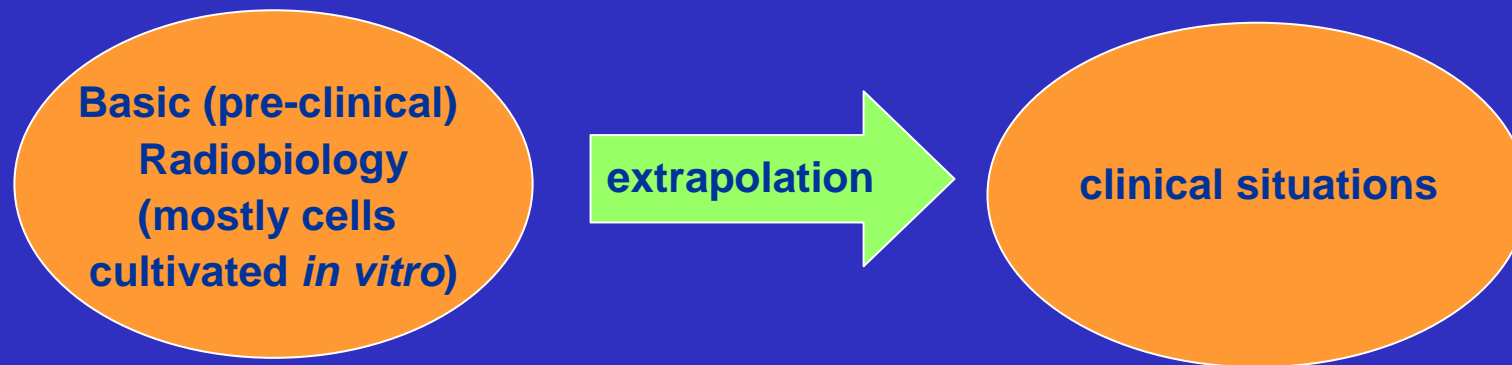


The frequency of ionization clusters in any DNA segment is calculated by a track structure simulation code (Moca 15) at microscopic level for each component (coupled to another Monte Carlo code describing the particle transport at macroscopic level across matter)

The “clinical” RBE

In treatment planning the general problem is to determine the “clinical” RBE to be taken into account in programming the dose. The objective is to allow the passage from physical to “clinical” or “biological” dose and vice versa, taking into account both tumour and healthy tissue characteristics

Search for the “clinical” RBE



Current solutions to the problem of finding the “clinical” RBE

Protons:

Use of an “overall” clinical RBE = 1.1 (no RB model)

Carbon ions:

- The GSI (Darmstadt) approach (based on the LEM)
- The NIRS (Chiba) approach (no RB model, based on comparison with clinical experience with neutrons)

The NIRS approach

At NIRS, where a passive system is used for the creation of the SOBP, an experimental approach is adopted:

a) experimental data are collected on RBE vs dose-averaged LET (measured for HSG and HeLa cells at 10% survival level) to obtain a “virtual biological” dose for HSG cells, uniform along the SOBP;

[Click here](#)

b) this data are combined with the beam modulation in such a way that a uniform “virtual biological” dose is obtained along the entire SOBP;

[Click here](#)

c) the “clinical dose” is then calculated using a normalization factor obtained from the comparison between the “clinical” doses and the “virtual biological” doses for NIRS neutrons; they were found to give the same biological effectiveness on HSG cells as the carbon beam in a position of the SOBP with average LET = 80 keV/μm.

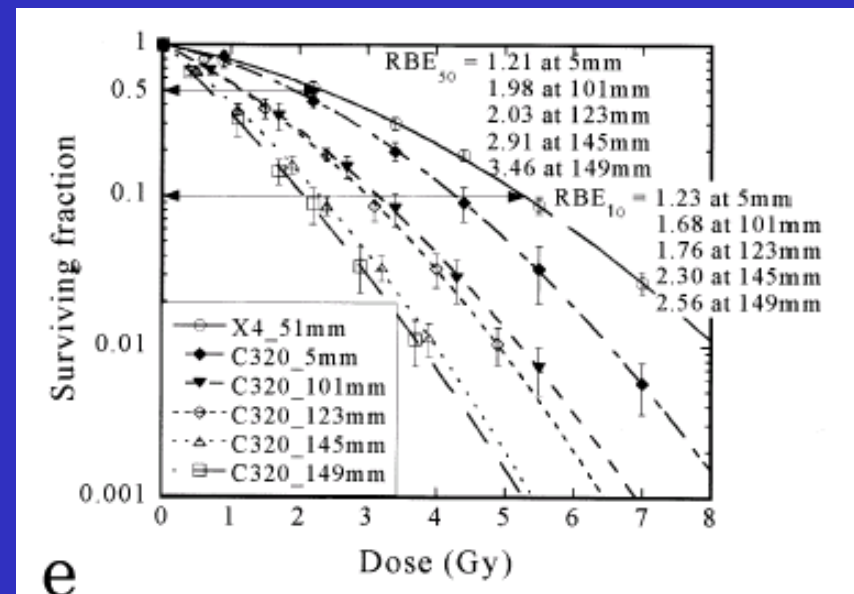
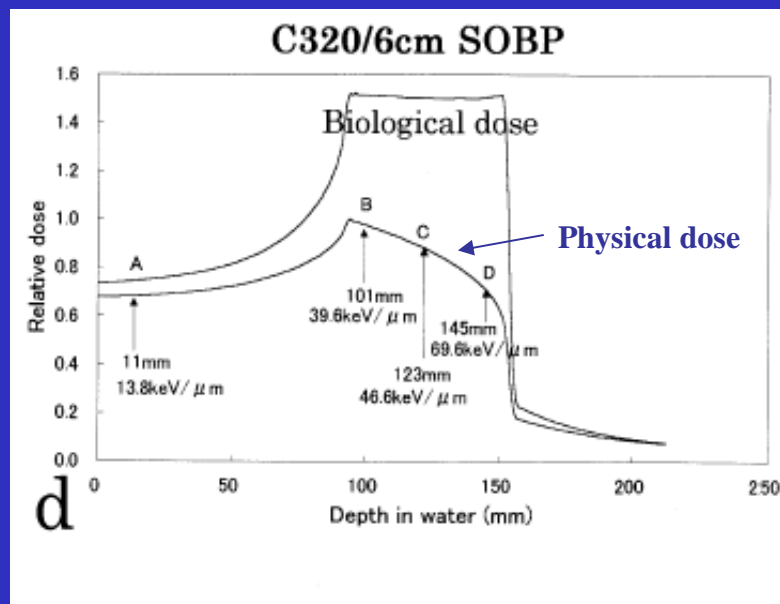
[Click here](#)

Details and updating can be found in *Kanai et al (2006)*, and references therein.

RBE of C ions changes along the SOBP

Depth-dose curves for a 6 cm SOBP generated by 320 MeV/u C beam at Hyogo: “physical” and “biological” doses

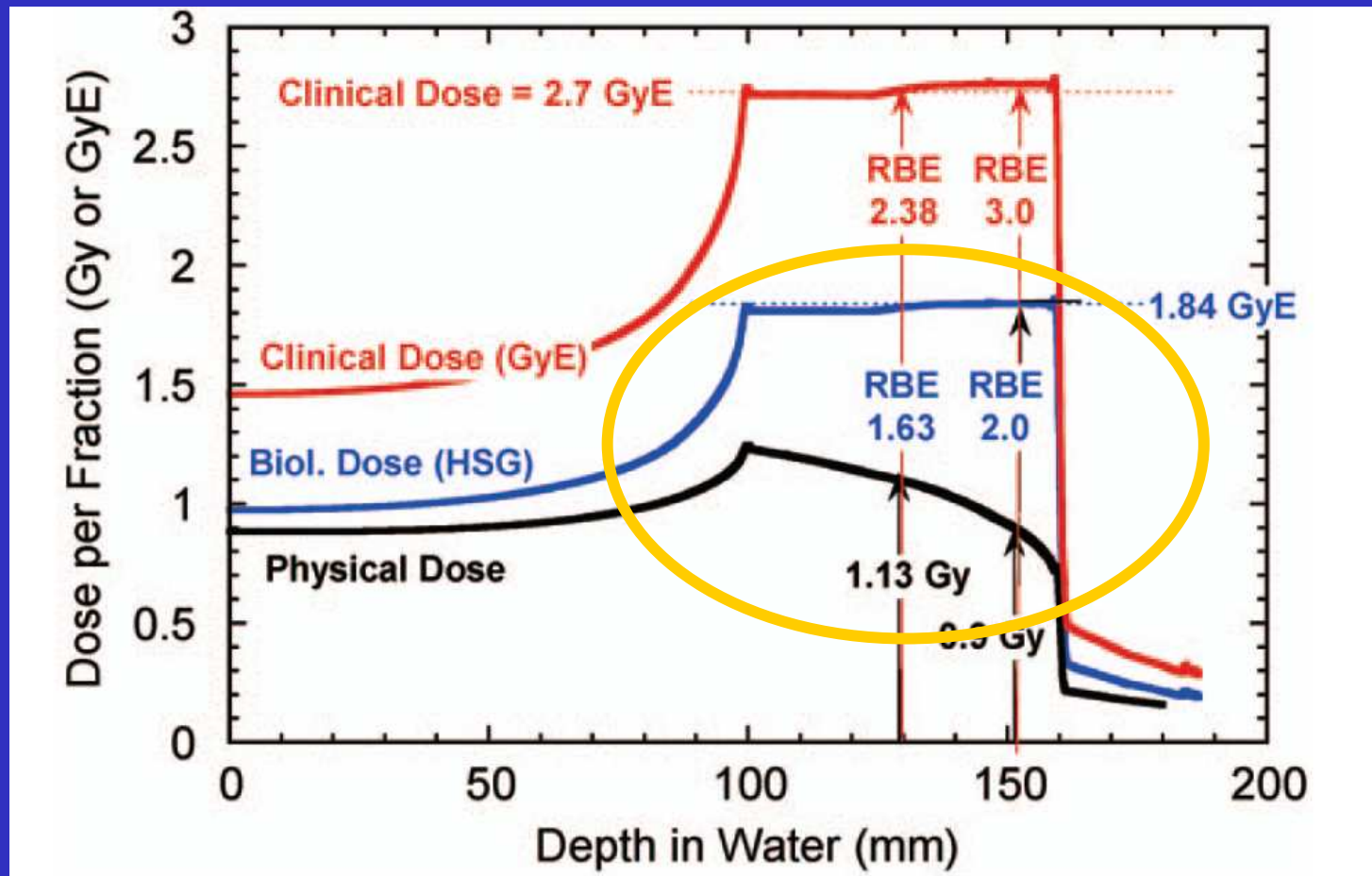
- Human Salivary Gland (HSG) cells
- cell survival and RBE at different positions in the 6 cm SOBP



From: *Kagawa et al. Preclinical biological assessment of proton and carbon ion beams at Hyogo Ion Beam Medical Center . Int.J.Rad.Onc.Biol.Phys.,2002*

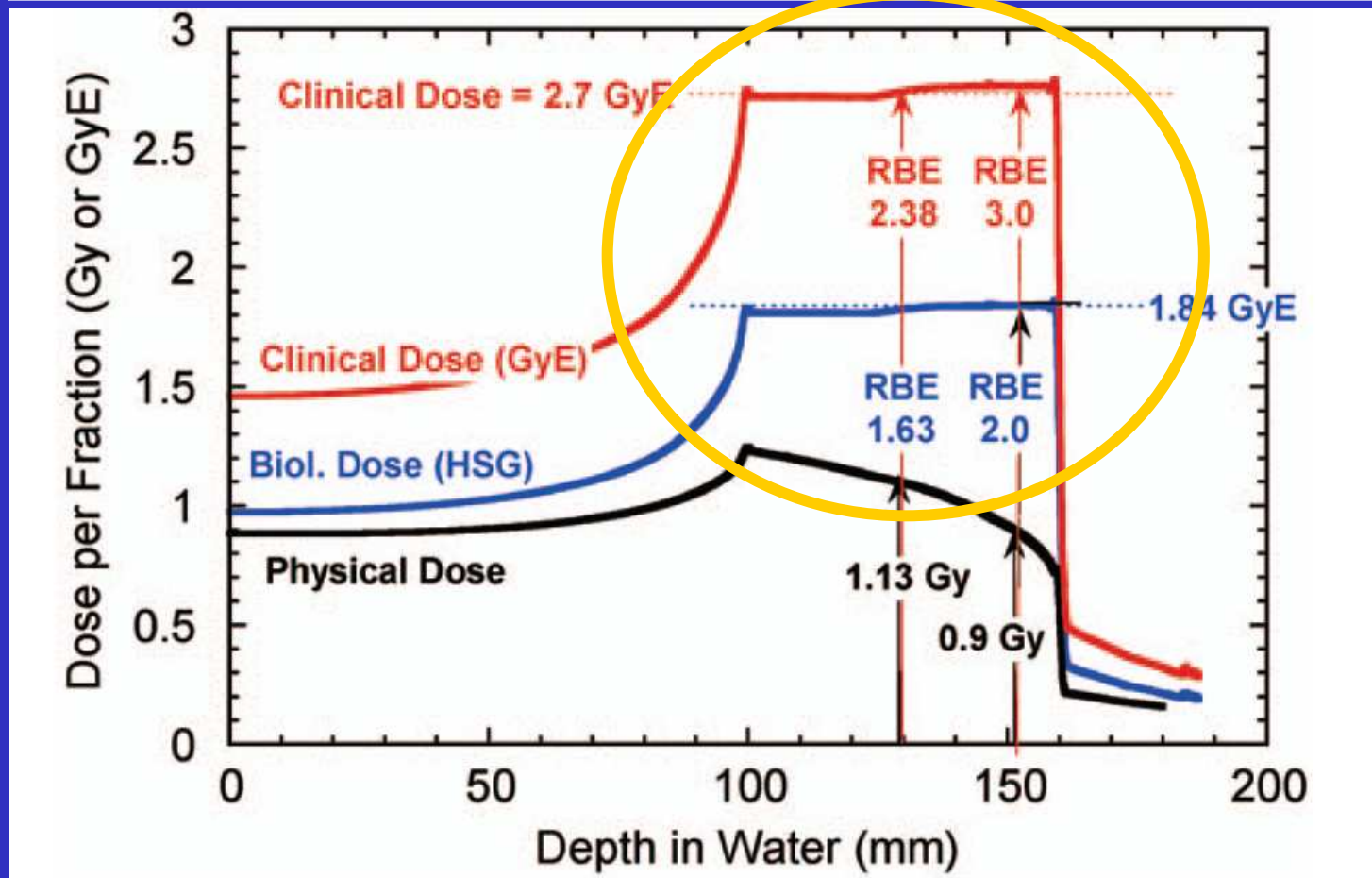
The NIRS approach: determination of clinical RBE at the center of SOBP

Depth-dose curves for a 6 cm SOBP generated by 290 MeV/u C beam at HIMAC: “physical”, “biological” and “clinical” doses



The NIRS approach: determination of clinical RBE at the center of SOBP

Depth-dose curves for a 6 cm SOBP generated by 290 MeV/u C beam at HIMAC: “physical”, “biological” and “clinical” doses



The GSI approach

At GSI an active system was adopted for the creation of the SOBP and a model-based approach was developed to evaluate the clinical dose.

A TPS based on this method is now in use at and HIT (Heidelberg) and is being used for the first trials at CNAO (Pavia).

It includes the following steps:

a) use of the Local Effect Model (LEM) to predict the *in vitro* (biological) response to various cell lines and ion beams;

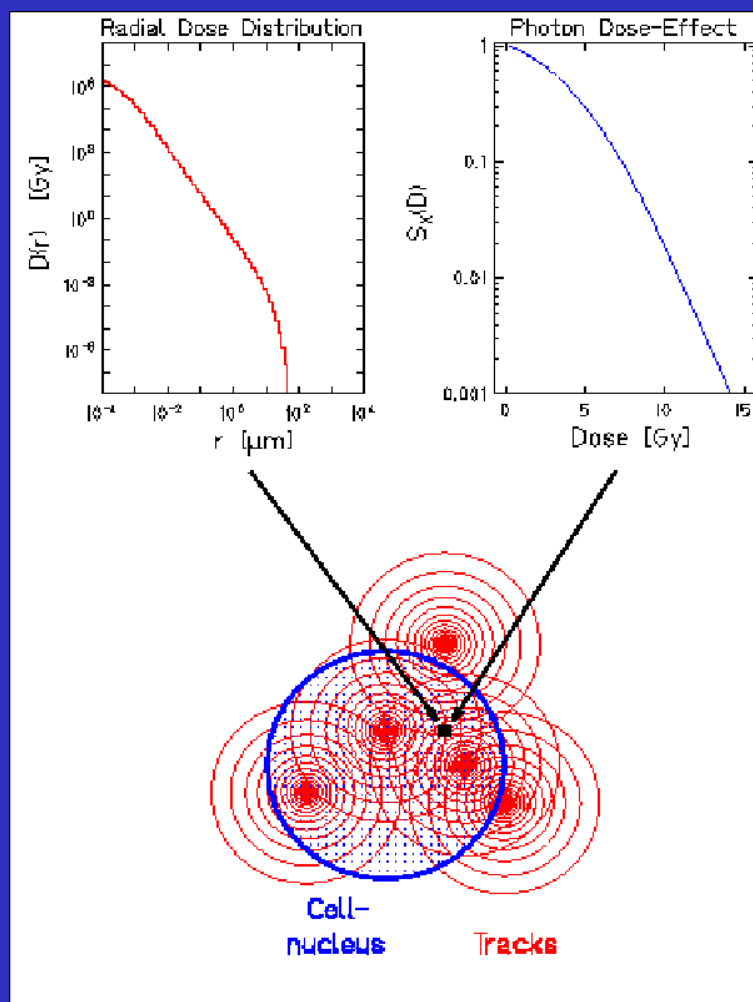
b) the “clinical” response is obtained by assuming that the tissue under consideration and the *in vitro* system have the same RBE if they have the same ratio α/β (the linear and the quadratic coefficient of the survival curve, respectively);

c) algorithms and codes have been developed to calculate the effects of mixed fields.

Details and updating can be found in *Krämer and Scholz (2006)*, and references therein.

Il modello LEM

Local Effect Model (LEM) (Kraft and Scholz).



Predizione degli effetti di particelle cariche.

Applicazione agli ioni carbonio usati in adroterapia

Viene calcolato il profilo radiale di ciascuna traccia d'interesse.

Viene schematizzato il nucleo cellulare, considerato come sito sensibile.

Il nucleo è coperto dalle tracce delle particelle e in ogni pixel viene calcolato il contributo alla dose da parte di ciascuna traccia.

Per ciascun pixel tali contributi sono sommati e viene calcolata la probabilità d'inattivazione sulla base della curva di sopravvivenza misurata con raggi X.

La probabilità d'inattivazione totale è calcolata per integrazione sul nucleo delle probabilità nei singoli pixel.

Il modello LEM

Local Effect Model (LEM) (Kraft and Scholz).

La probabilità di sopravvivenza per una singola cellula è legata al numero di eventi letali N_{let} :

$$S_{lon} = e^{-N_{let}}$$

con

$$N_{let} = \int_x \int_y \int_z \frac{-\ln S_x(D(x,y,z))}{V} \cdot dx dy dz$$

$D(x,y,z)$ indica la reale dose locale depositata nella posizione (x,y,z) definita dalla somma delle dosi locali provenienti da tutte le tracce che contribuiscono a questa posizione specifica, e V è il volume del bersaglio critico, il nucleo cellulare.

Metodi Monte Carlo sono usati per simulare la distribuzione spaziale degli attraversamenti delle particelle, e la sopravvivenza di una popolazione è determinata come la probabilità di sopravvivenza media delle singole cellule

Carbonterapia: l'esperienza del NIRS (Chiba)

Clinical experiences have demonstrated that C-ion RT is effective in such regions as the **head and neck, skull base, lung, liver, prostate, bone and soft tissues, and pelvic recurrence of rectal cancer**, as well as for histological types including **adenocarcinoma, adenoid cystic carcinoma, malignant melanoma and various types of sarcomas**, against which photon therapy are less effective. Furthermore, when compared with photon and proton RT, **a significant reduction of overall treatment time and fractions** has been accomplished without enhancing toxicities

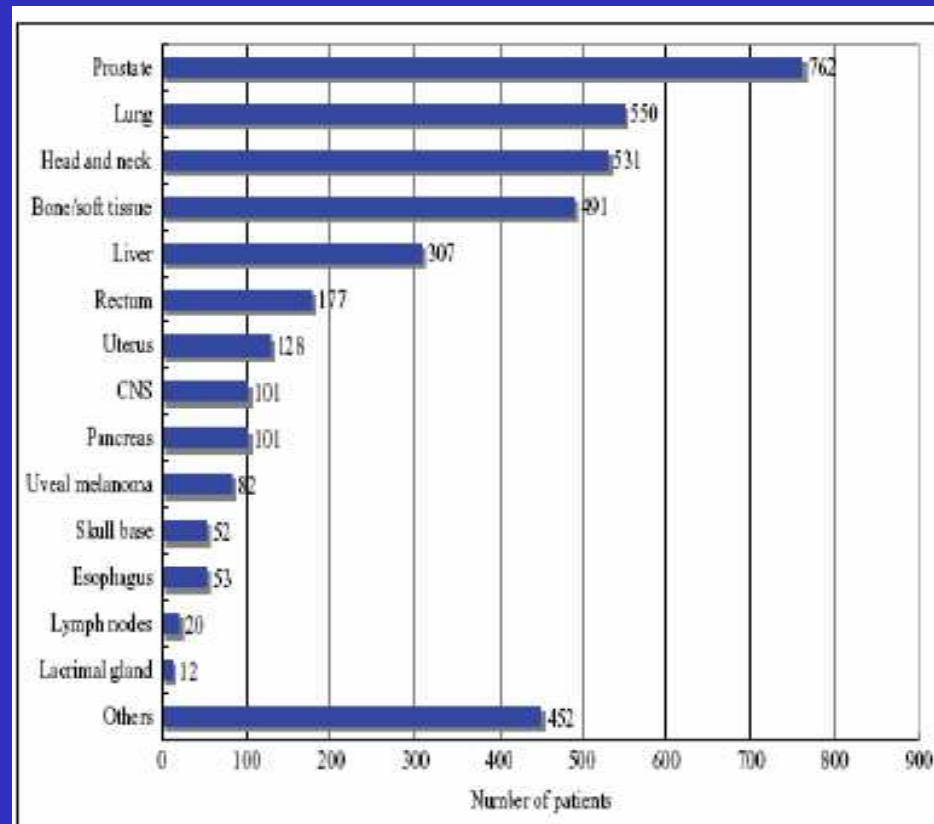


Figure 1. Number of patients, with a variety of tumors enrolled at NIRS for C-ion RT.

NIRS annual report
2008, Tsujii et al.

Some criticisms to high-LET radiotherapy

From: Michael Goitein, Convegno SIRR, Trento 2008

High-LET affects not only the RBE, e.g:

- **Decrease oxygen enhancement ratio (OER)**

- good for tumor, **advantage** for high-LET

- **Reduce repair**

- bad for normal tissues, **disadvantage** for high-LET

- **Reduce cell-cycle dependence (decrease resistance)**

- bad for normal tissues, **disadvantage** for high-LET

Therefore, the use of high-LET is a research matter at this time. ^{12}C ions should only be used in the setting of clinical trials (M. Goitein).

This viewpoint is not shared by the many radiotherapists who are involved in carbontherapy.

**Understanding correlation between:
radiation quality,
DNA damage,
cell killing and other relevant end
points
is the present challenge for
developing general treatment plans**

Searching correlation between cell killing and DNA damage

There is good evidence that **Double Strand Breaks (DSB)** are the critical lesions for cell killing and other cellular endpoints.

However, the **RBE for DSB induction** does not mirror the LET dependence of RBE for cell killing.

By contrast, the RBE for **residual DSB** (e.g., evaluated after rejoining/repair) is LET dependent.

Correlated lesions and repairability

- High-LET particles generate clusters of spatially correlated lesions in cellular DNA
- Complex lesions are more severe because they are more difficult to be repaired by the cell machinery
- Simulations by Monte Carlo codes have indicated that the energy deposited in a region where a DSB occurred increases with LET (increase of lesion complexity)

Perspectives

- **There a wide general consensus in that there are different indications for p and C-ions**

But some contrasting voices exist: “Biologically, we have no idea whether ^{12}C ions will be better or worse than protons; they could be better (e.g. better tumor control), BUT they could be (much) worse (e.g. late NT effects)” (*M. Goitein*)

- **Devoted research (especially for C-ions) are needed to assess all the aspects of the radiobiological potential of charged hadrons and its transferability to clinics**
- **Research structures should be implemente at the therapy centres with devoted facilities, such as experimental radiobiological areas and, when possible, experimental beam lines.**

The end.....

**It is a capital mistake to theorize before one has data.
Insensibly one begins to twist facts to suit theories,
instead of theories to suit facts.**

(A Scandal in Bohemia, Arthur Conan Doyle)