UT Southwestern Particle
International Workshop on Particle Therapy Research
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UT Southwestern Medical Center, Dallas, Texas

Clinical Experience of Carbon-Ion Radiotherapy

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Progress of radiotherapy

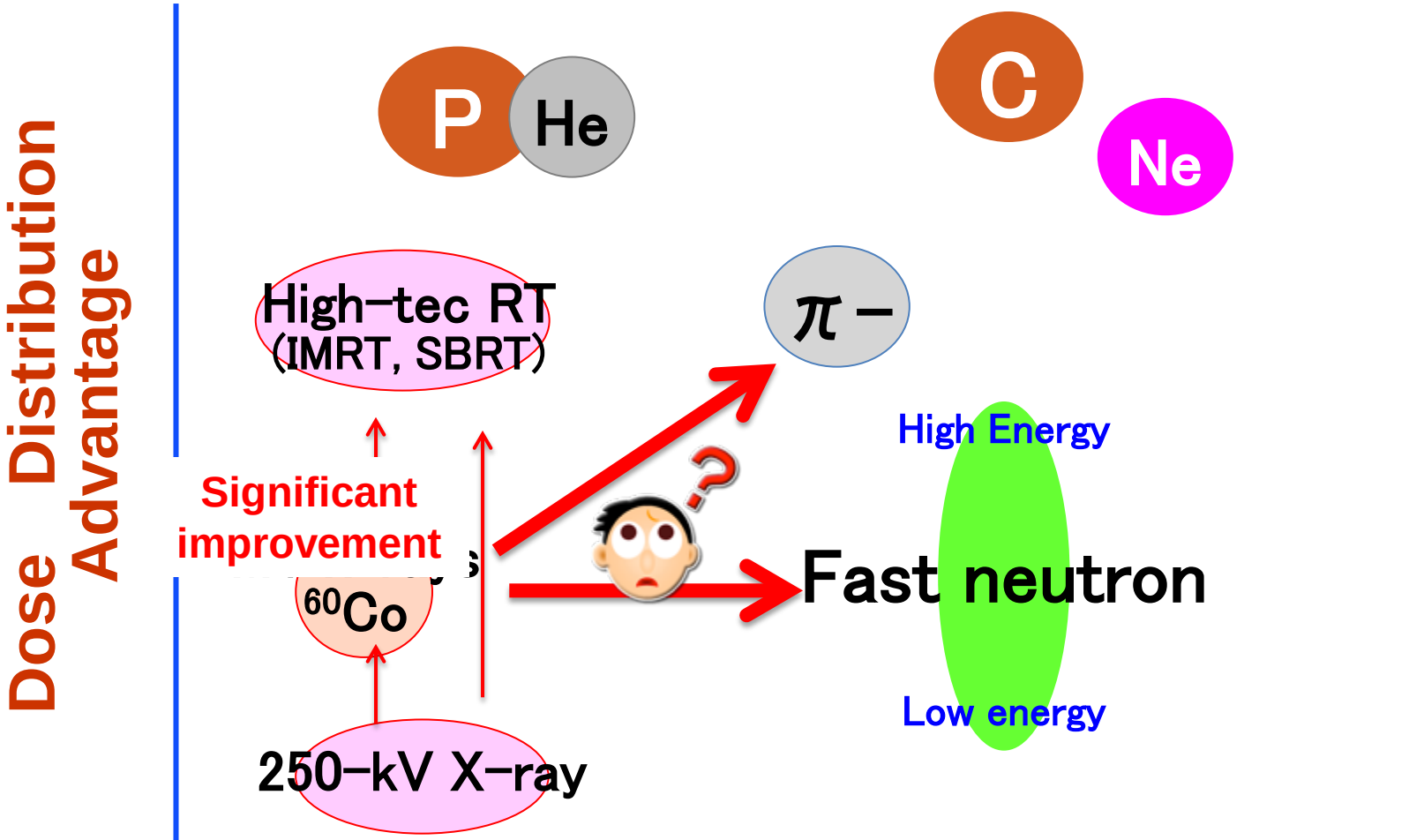
- **Success of radiotherapy depends largely on the performance of accelerators, treatment planning system and related devices.**
- **This is particularly so when we notice the fact that the photon energy reaching the order of MV in 1950s contributed significantly to the improvement of treatment outcomes.**

Improved survival in several types of cancer with megavoltage therapy

Type of Cancer	5-yearsurvival(%)	
	kV X-rays	MV X-rays
Hodgkin's disease	30—35	70—75
Ca. of the cervix	35—45	55—65
Ca. of the prostate	5—15	55—60
Ca. of the nasopharynx	20—25	45—50
Ca. of the bladder	0—5	25—35
Ca. of the ovary	15—20	50—60
Retinoblastoma	30—40	80—85
Seminoma of the testis	65—70	90—95
Embryonal ca. of the testis	20—25	55—70
Ca. of the tonsil	25—30	40—50

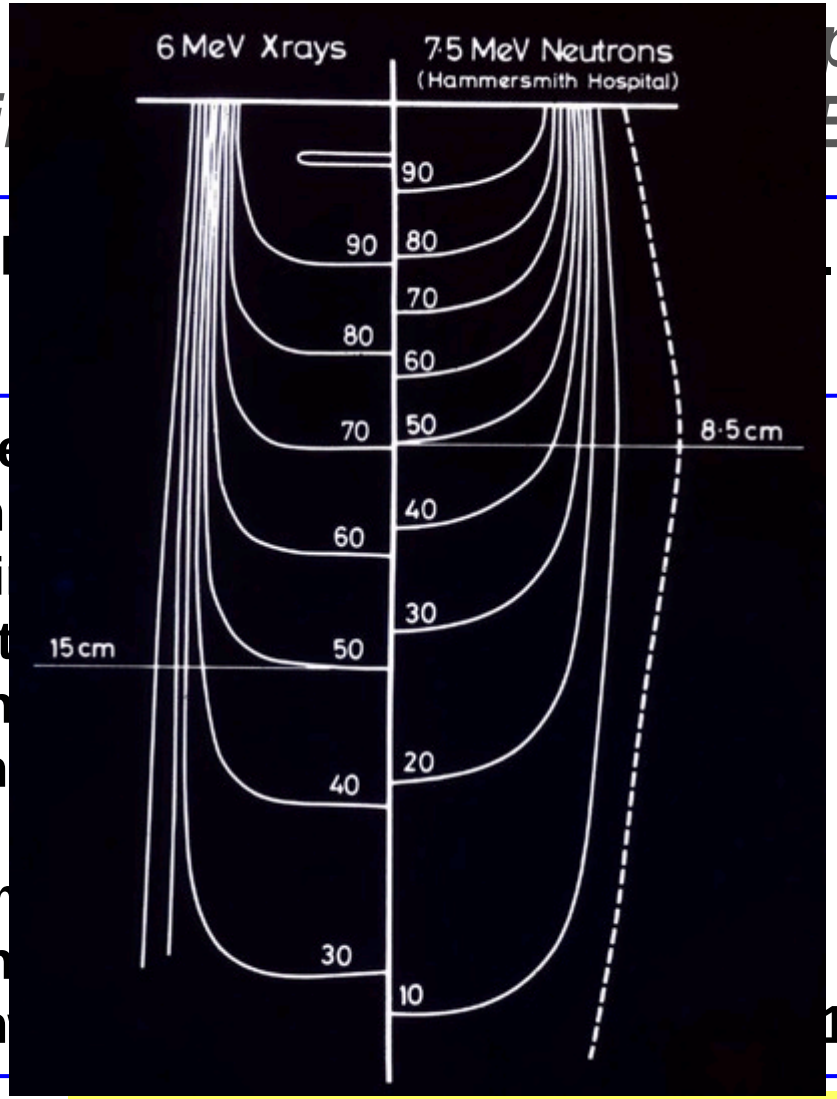
Report of the Panel of Consultants on the Conquest of Cancer. Washington, D.C., U.S. Government Printing Office, 1970.

Dr Raju's idea demonstrating the relative advantage of particles (1974)



This idea of representing the relative merits of particles was suggested by Mr. A. M. Koehler(Raju et al., 1974b).

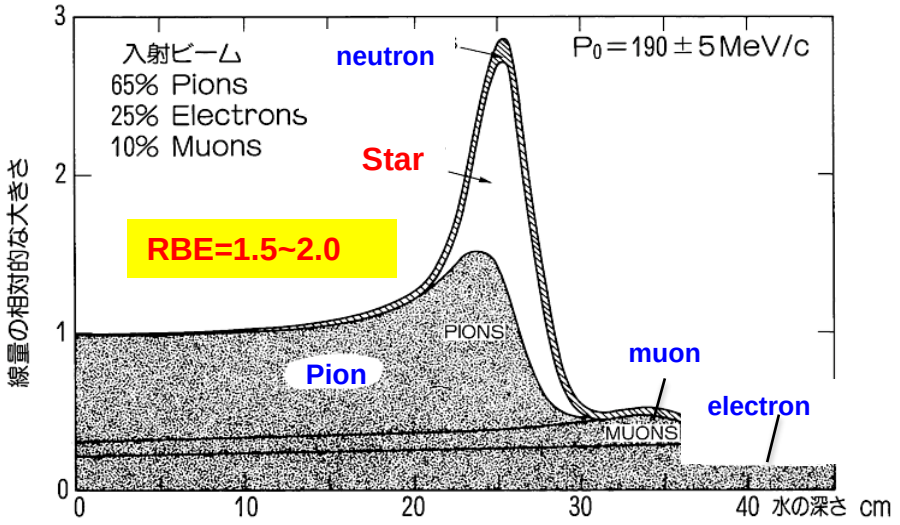
...plications and Survival ...Bone/Soft Tissue Sarcomas



Auth...	Cont-rolled	Major Compl.	Survival
Cate...	75%	32%	-
Orn...	65%	-	-
Sali...	62%	12%	59%(5-62mo)
Batt...	36%	27%	-
Coh...	47%	38%	39% (>2yr)
Sch...	50%	-	-
	50%	33%	-
War...	18%	18%	-
Dun...	38%	50%	-
Sch... 1	50%	-	-

Severe complications were unacceptably high in relative to modest local control, most likely attributed to poor dose distributions.

Pion Therapy



線量は粒子の飛程の終わり近くで最高となるが、その深さはパイオンの最初のエネルギーにより決まる。線量が最高になるところをブラグピークと呼ぶ。がん組織に丁度ブラグピークが当るように照射条件を整えることによりがん組織のみを殺すことが出来る。

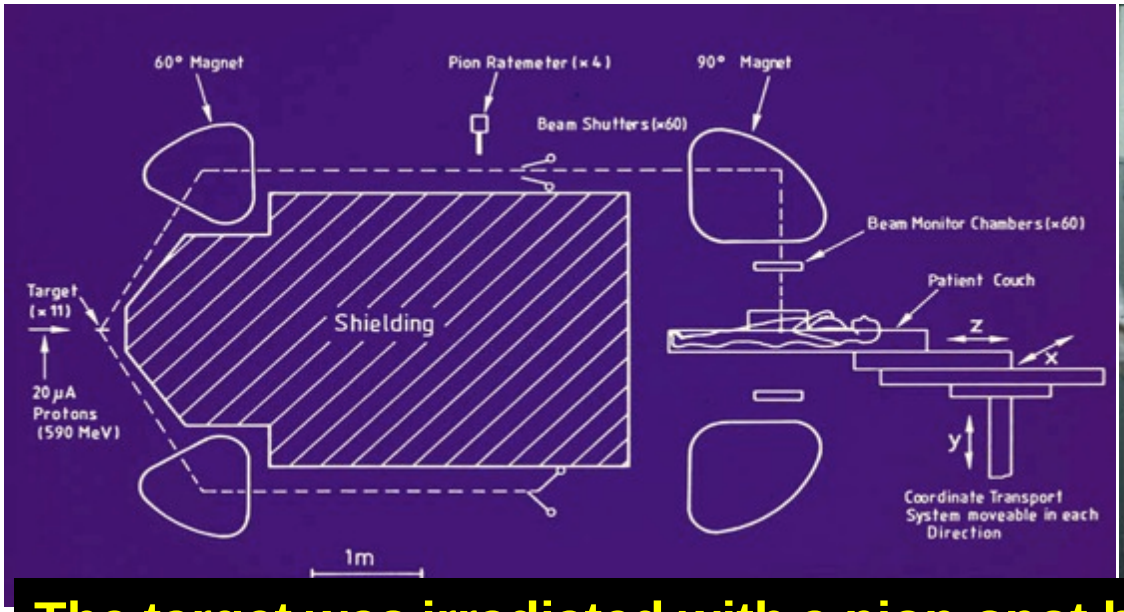
図１　パイ中間子の深部線量分布

11-6-1-10-2

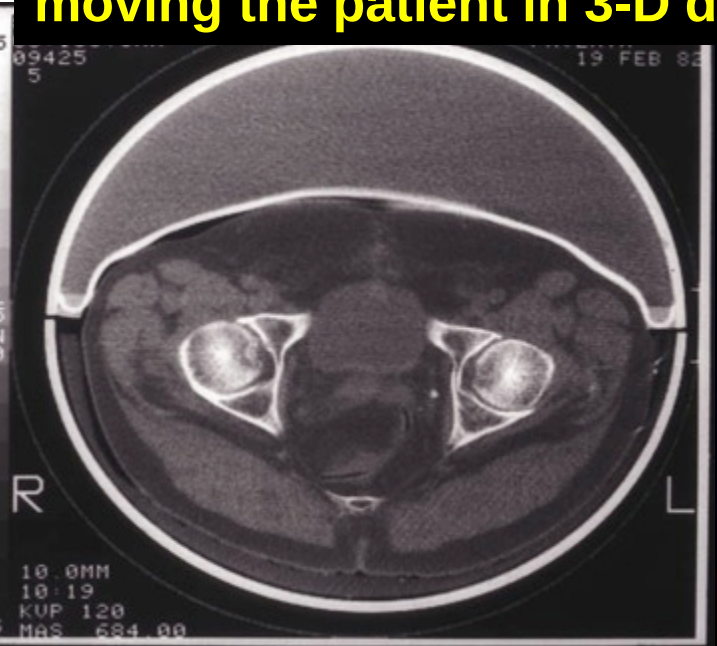
Los Alamos (LAMPF)

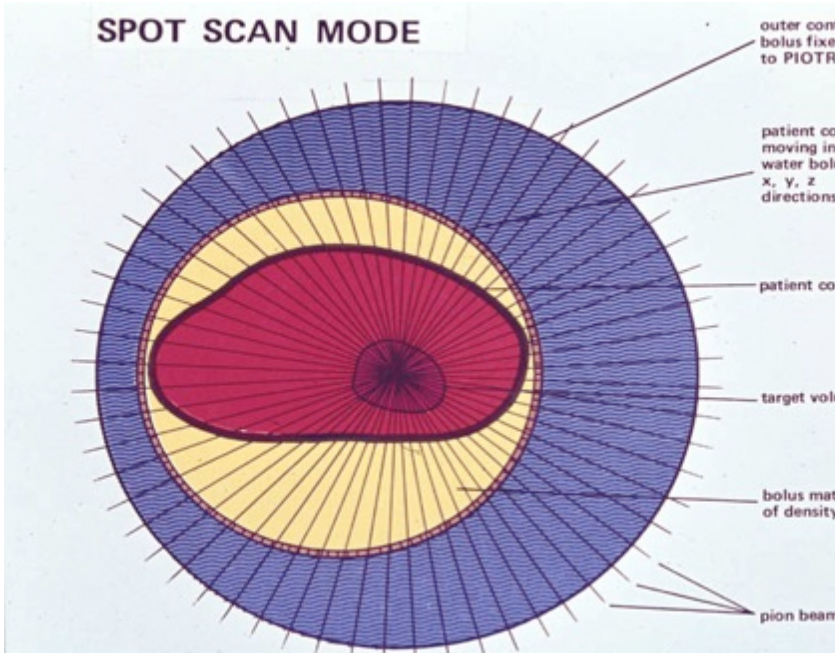
Facility	Country	Accele-rator	Energy (MeV)	Period	No. patients
LAMPF	USA	Linac	600	1974~82	230
TRIUMF	Canada	Cyclotron	500	1979~94	367
PSI	Switzer-land	Cyclotron	500	1980~93	503
				Total	1,100

Body moving scanning was developed at PSI, Switzerland



The target was irradiated with a pion-spot by moving the patient in 3-D dimentions.



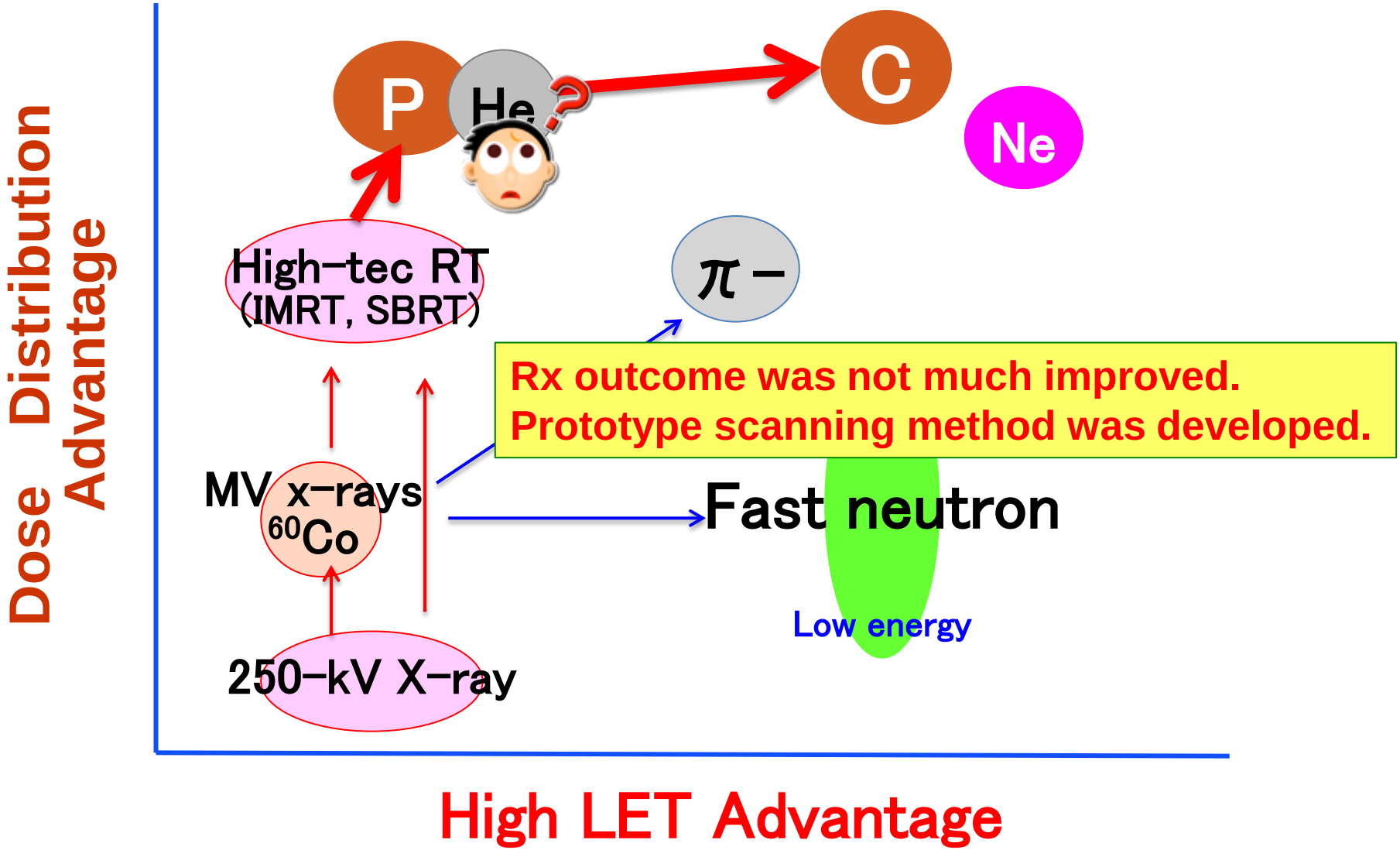


Results of Pion Therapy in Los Alamos (LAMPF)

Tumor Site	No. Patients	Local Control		Severe Complication
		Failure	Success	
Head & neck	31	23	7 (30%)	1
Lung	6	6	1 (17%)	
Pancreas	17	17	0	
Colon	12	9	0	3
Uterus	4	3	1 (25%)	
Urinary bladder	4	2	1 (25%)	1
Prostate	21	3	12 (57%)	6
Glioma (Grade3)	15	12	2 (13%)	1
Glioma (Grade3)	14	14	0	
Others	5	5	0	
Total	129	93 (72%)	24 (19%)	12 (9%)

Because expected results were not provided as for the local control and toxicities, pion therapy was discontinued.

Dr Raju's idea demonstrating the relative advantage of particles (1974)



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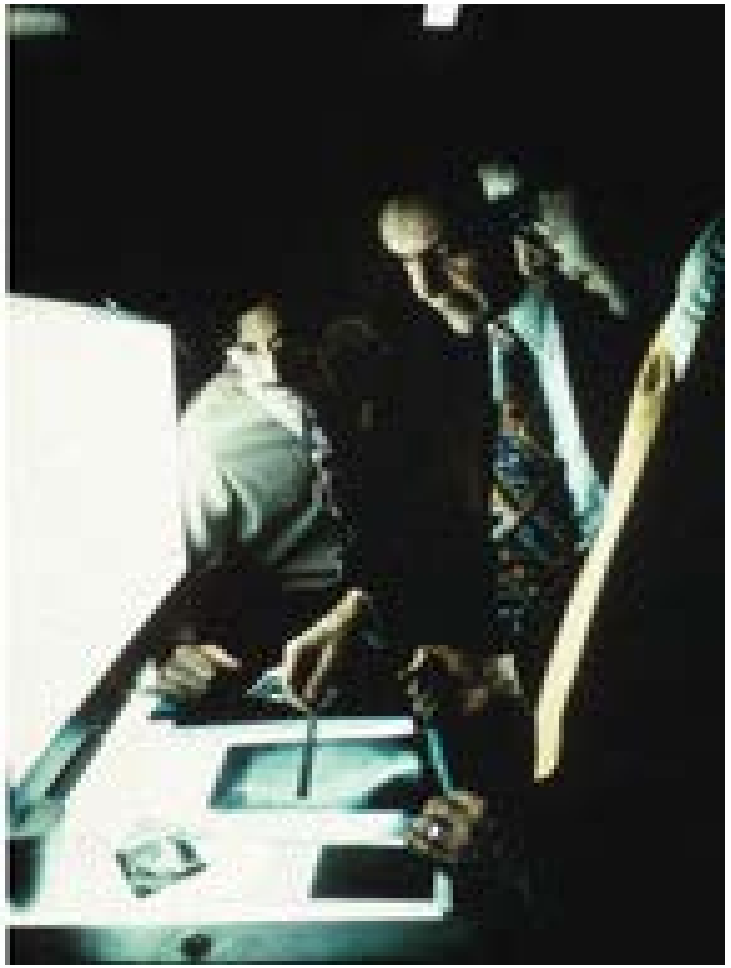
Checking Portal Film on 1st Patient Fractionated PRT



Courtesy of H.SUIT

Fractionated proton therapy was pioneered by H.Suit, MGH.

With invention of CT scans in 1973, accurate calculation of the beam path and dose distribution became possible.

Definite advantage of superior dose distribution with proton beams

- **Superior dose distribution with protons has enabled delivery of sufficient dose to the tumor while reducing the dose to the normal tissues in many tumors.**

  → Reduction of side effects and secondary cancer

- **Clinical trails are being conducted to confirm the advantage of proton therapy in selected tumors.**

Recent Announcement by Blue Cross-Blue Shield of California

PBT medically necessary

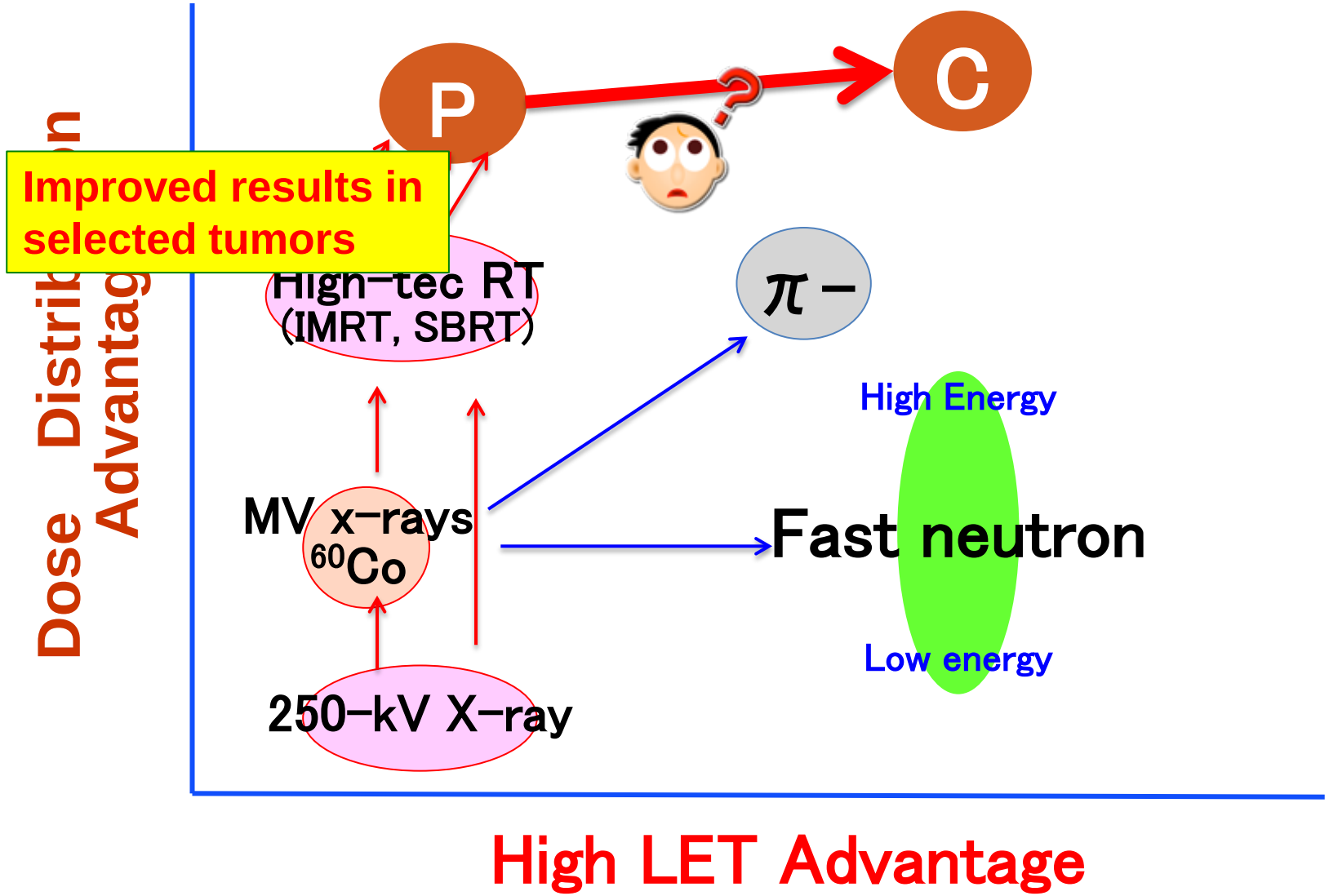
- **Intraocular melanoma**
- **Skull base chordoma and chondrosarcoma**
- **Pediatric tumors**
- **Head and neck cancer**

PBT investigational : only covered if part of a clinical trial

- **Lung cancer**
- **Unresectable pelvic tumors**
- **Left breast cancer**
- **Unresectalbe GI cancers:**
  Liver, biliary, anal, and rectal cancer
- **Prostate cancer**

Kerstiens et.al. Proton therapy expansion under current United States reimbursement models IROBP 89: 235-240, 2014

Dr Raju's idea demonstrating the relative advantage of particles（1974）



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Mutation spectrum

Flower mutation of carnation regenerated from leaf cultures treated with different mutagen

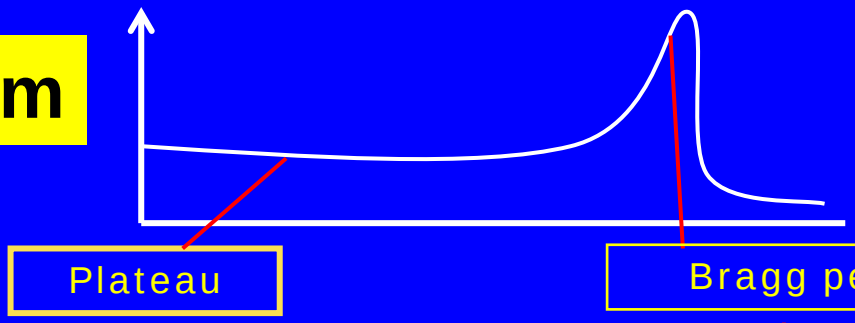
Mutagen	Mutation frequency ($\times 10^{-1}$ %)											
	Flower color										Shape	
	Light pink	Pink	Dark pikn	Red	Salm-on	Yel-low	Cream	Stripe	Minute striped	Com-plex	Round petals	Dianthus type petals
EMS	0	5.2	0	1.0	0	0	0	3.1	0	0	0	0
Soft X-rays	1.7	8.4	0	3.4	0	0	0	0	0	0	0	0
Gamma-rays	1.7	2.6	0	1.7	0	0	0	0	11.3	0	0.9	0
Carbon ions	2.4	4.7	2.4	3.5	2.4	2.4	1.2	3.5	0	2.4	4.7	2.4

Commercialized in 2002 EU & Japan ($ 13 million in 2008)

Mutation spectrum of carbon ions was wider than the other mutagen

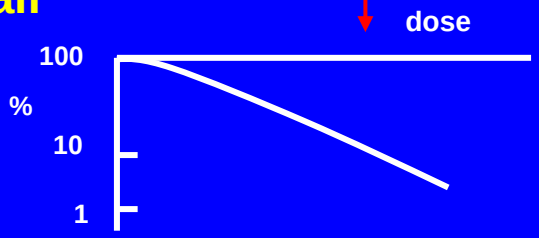
Okamura *et al.*, NIMB 206, 574-578 (2003).

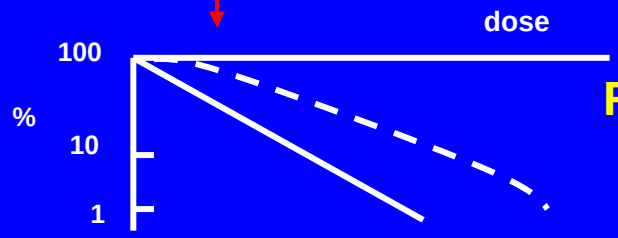
Carbon beam



RBE: 2~3.5

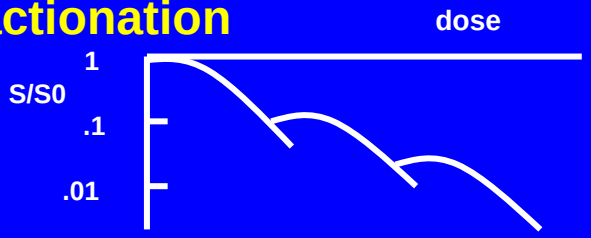
Repair

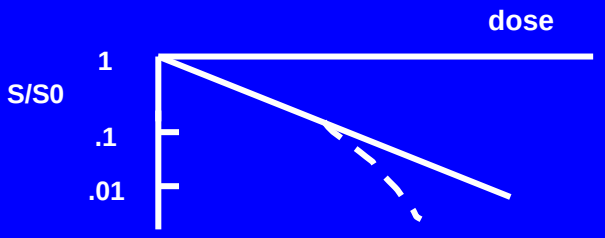




Repair is smaller

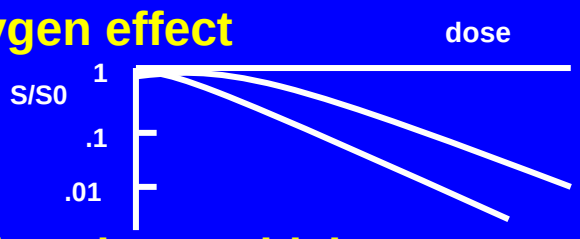
Fractionation

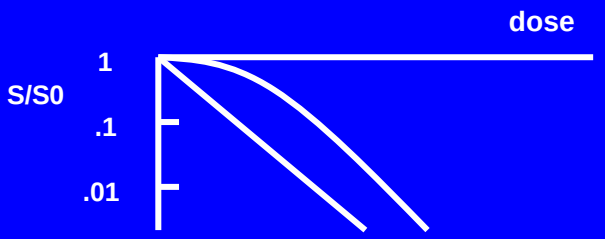




Effect from fractionation is smaller

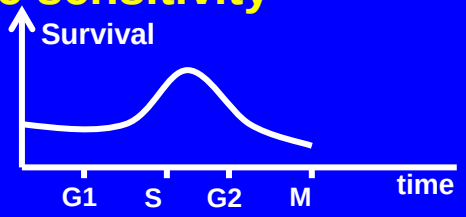
Oxygen effect

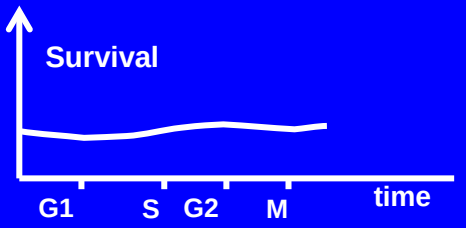




OER is smaller

Cell cycle sensitivity





Cell cycle difference of sensitivity is smaller

(Courtesy of Dr. Kraft)

Clinical Trials at LBNL/Bevalac, 1975–1992

J.R. Castro conducted clinical trials at LBNL.

1st He pat	06/75
1st C pat	05/77
1st Ne pat	11/77
1st Ar pat	03/79
1st Si pat	11/82

1975-1993

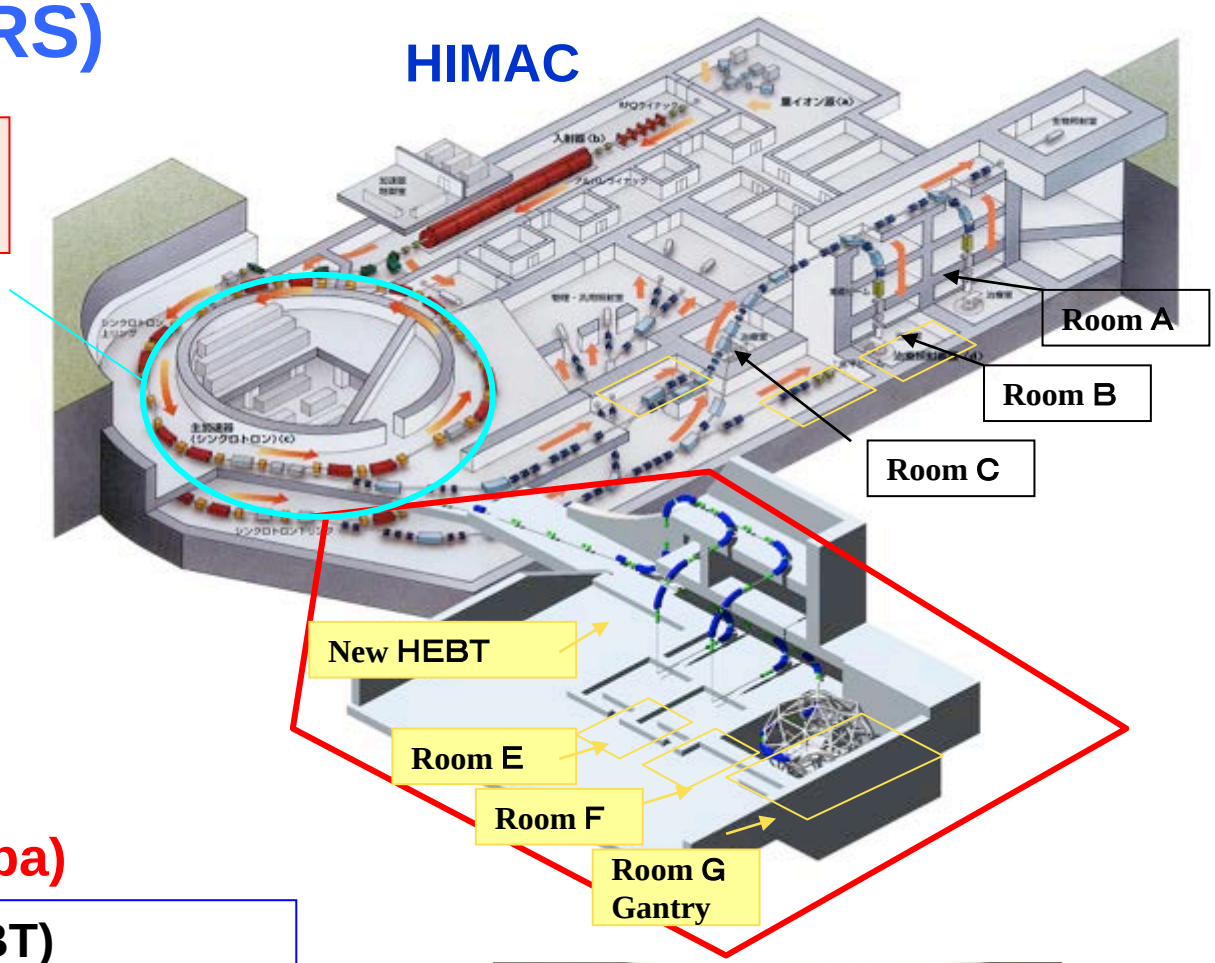
He ions = 2,054 pats

Neon ions = 433 pats

Other ions = 23 pats

HIMAC Facility (NIRS)

1994 Broad beam method
2011 Scanning beam method



A New Treatment Facility (Toshiba)

a. High energy beam transfer (HEBT)
a. Treatment rooms E & F
- Raster-scanning irradiation system
- Patient handling system with robotic arm bed

b. Treatment room G
- Superconducting rotating gantry

A New Treatment Facility

Building facade with green curtain

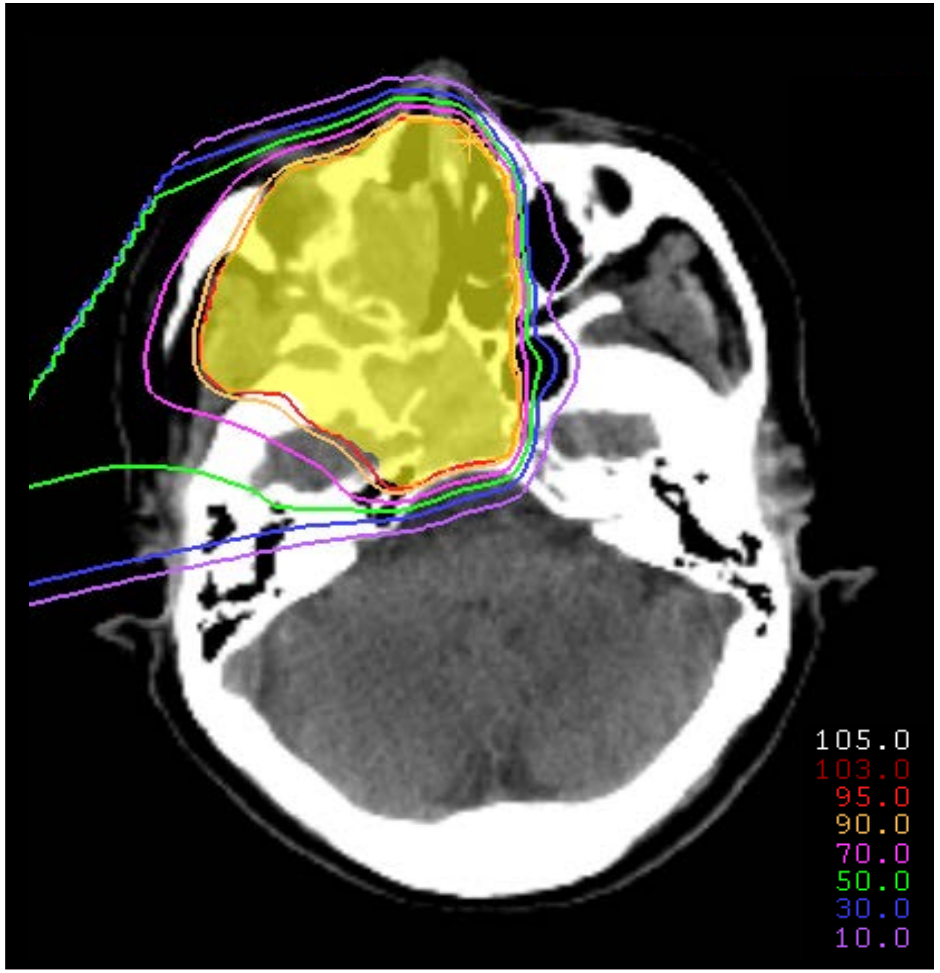
Entrance hall (1F)

Waiting hall (B2F)

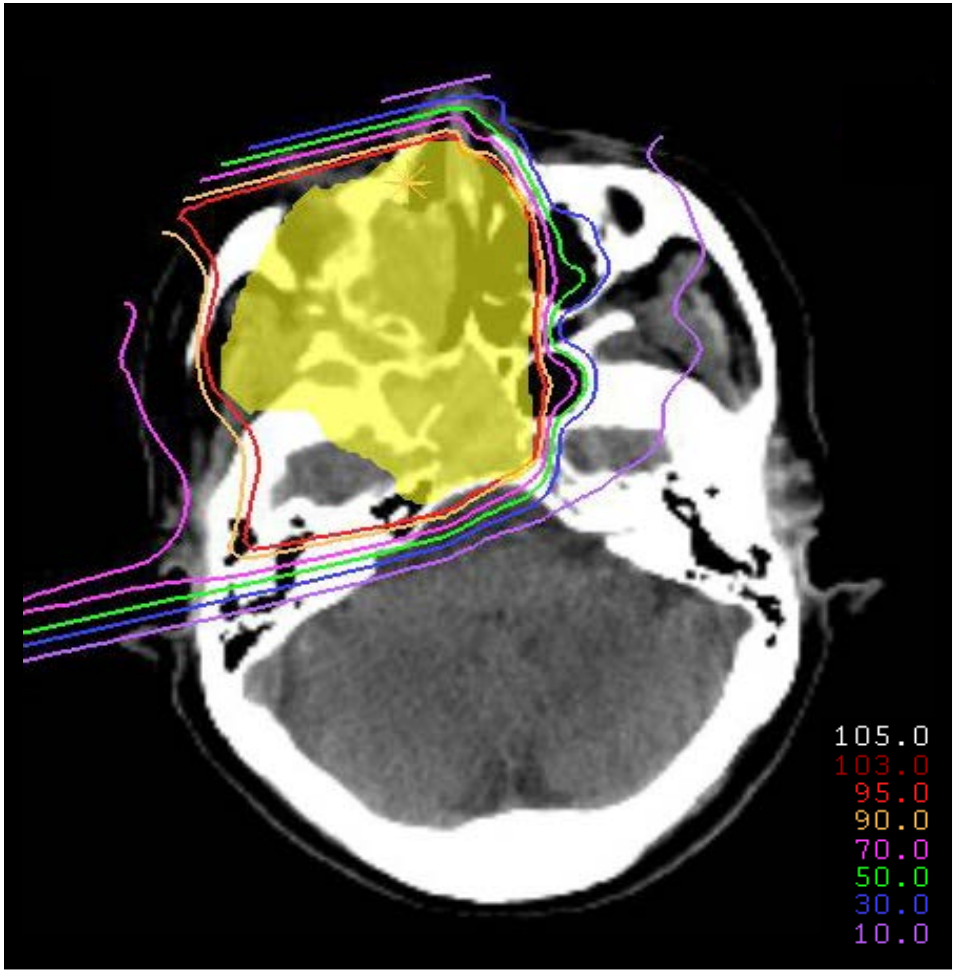
Treatment Room E (B2F)

Scanning and Wobbler

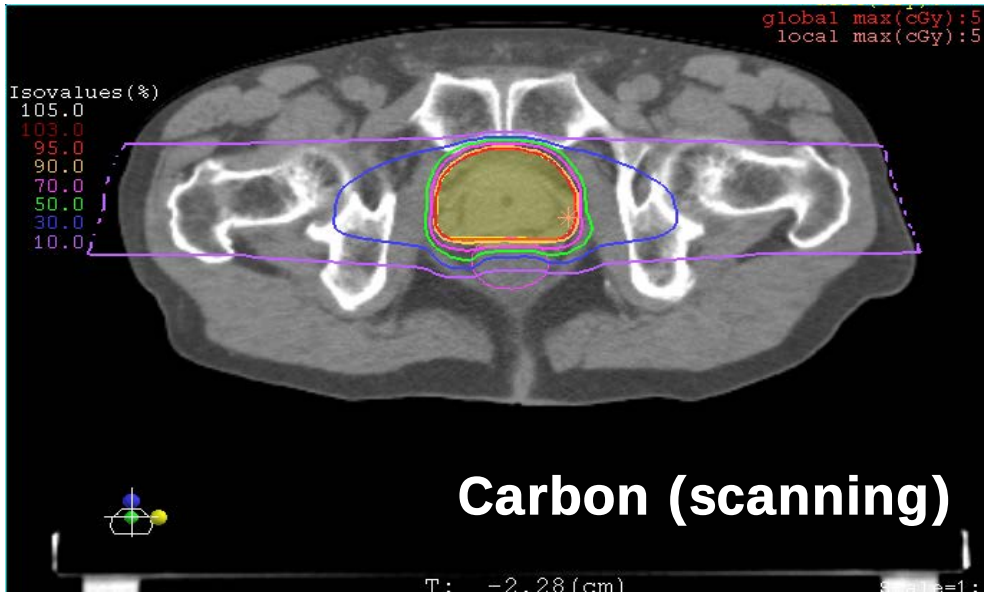
Scanning

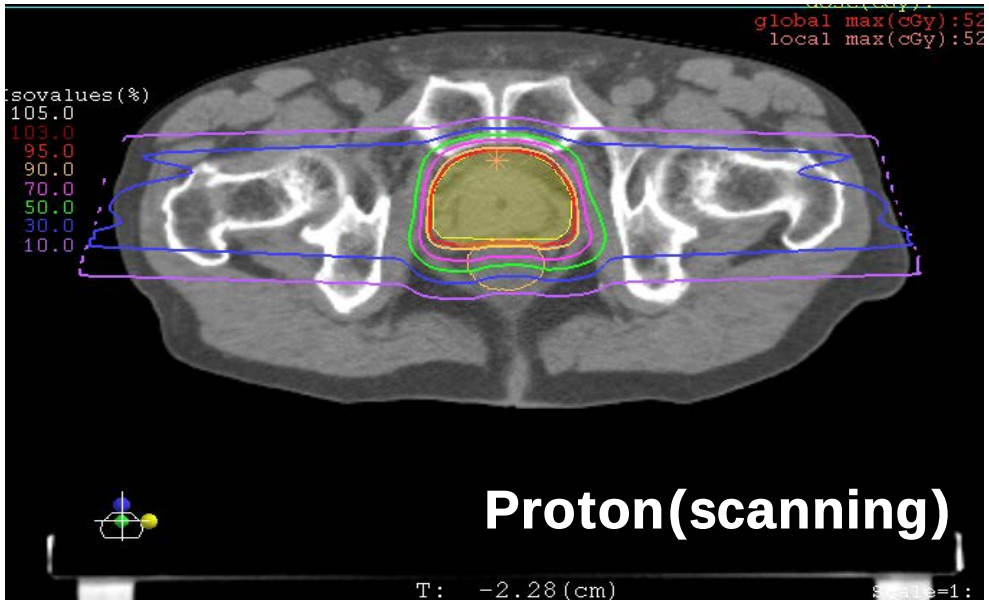


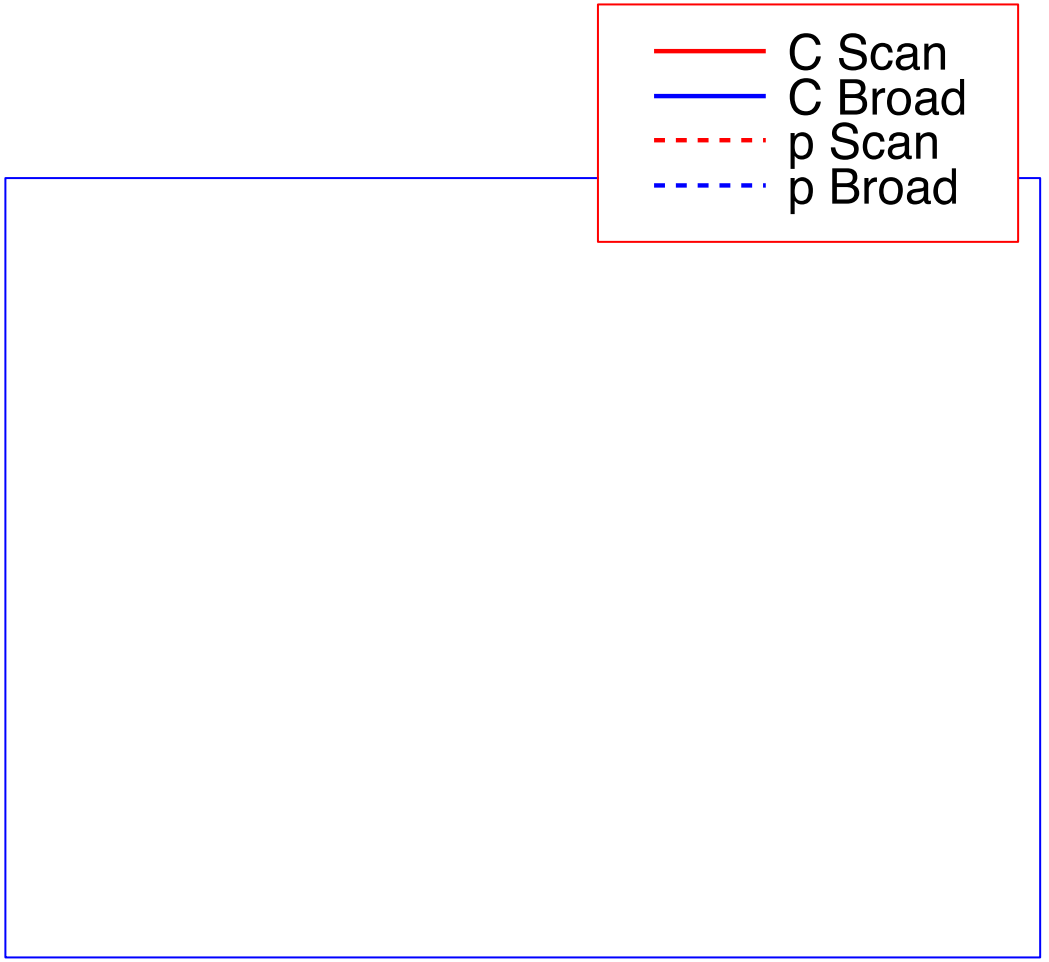
Wobbler



Comparative Treatment Planning; Carbon vs Proton / Prostate





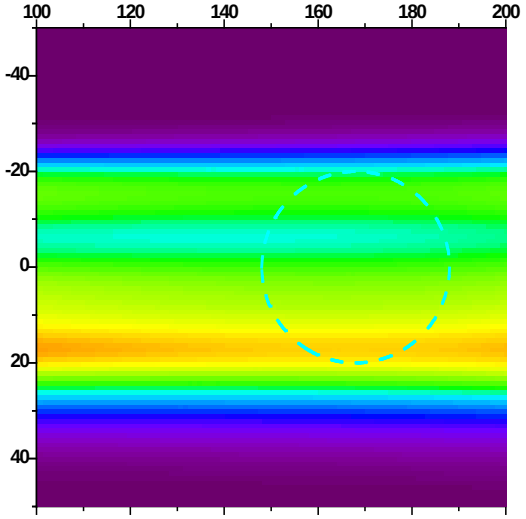


"These works were performed under research agreement with ELEKTA"

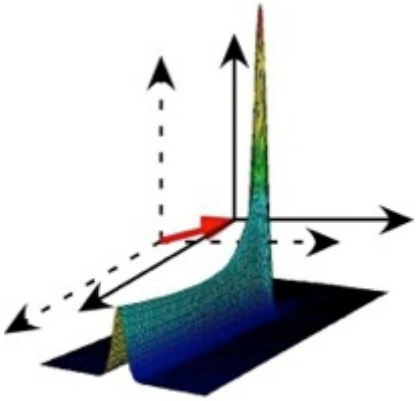
PET image of auto-activation in C-ion RT of prostate ca.

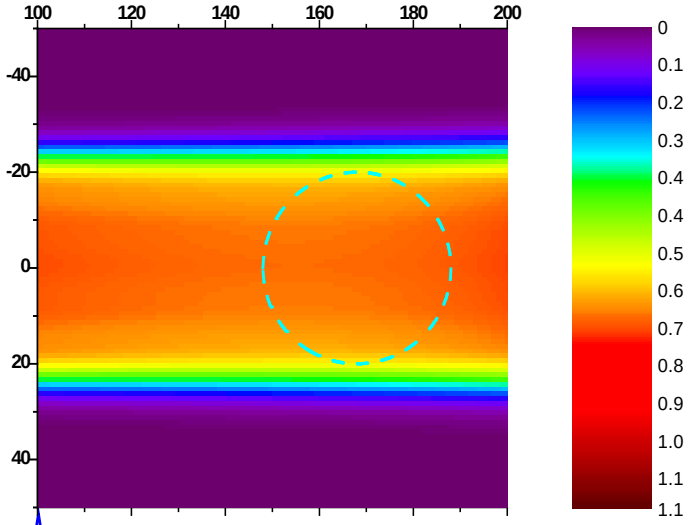
Fast Scanning for Moving Organs
NIRS approach

Simulation of moving tumor irradiation



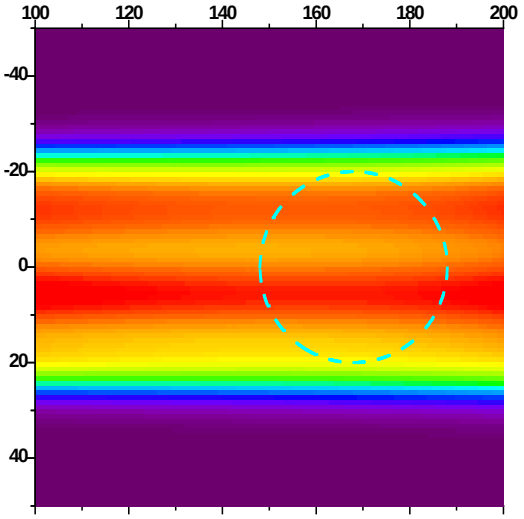
Non-gating





Gating with rescanning (8 times)

Gating

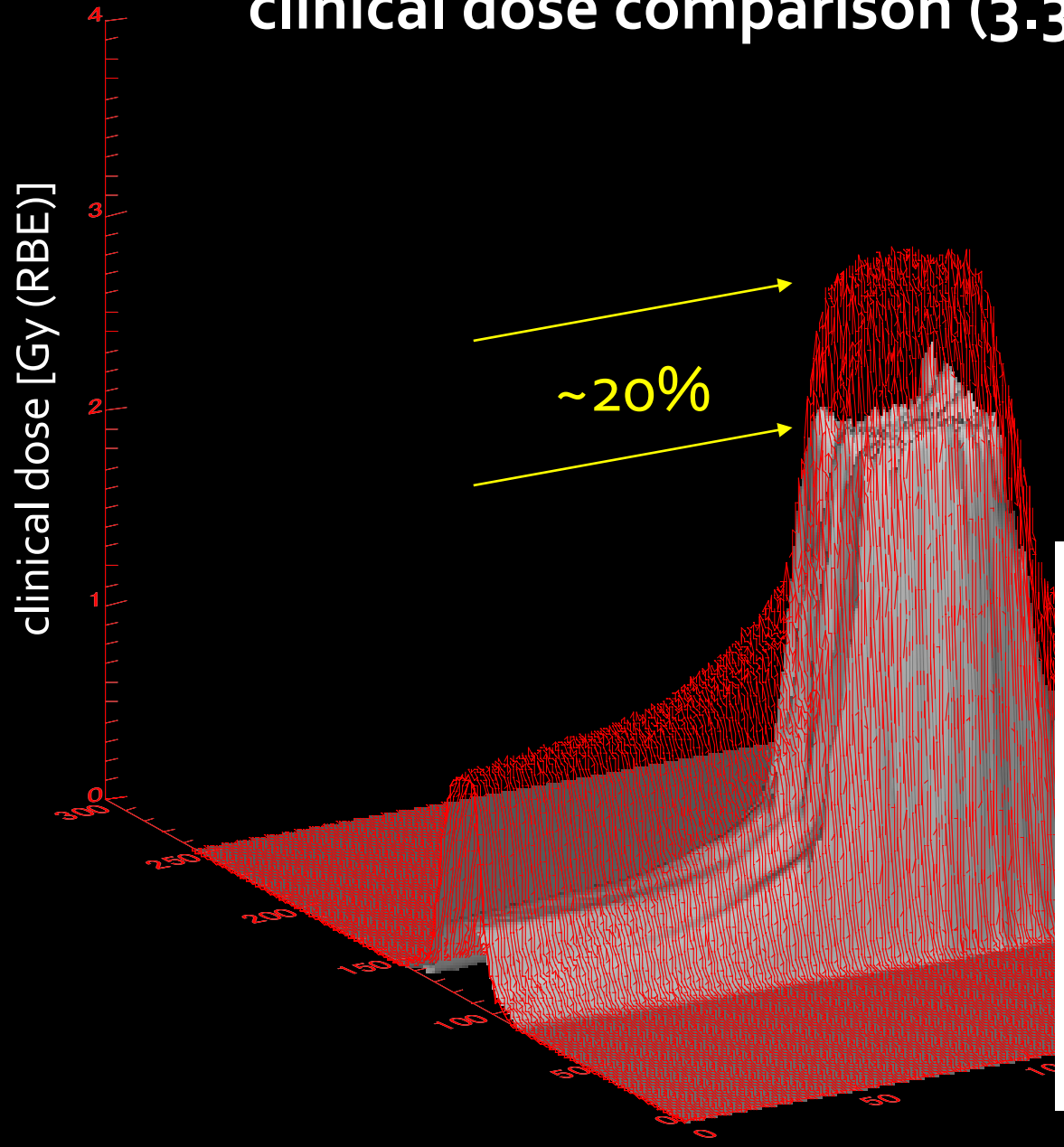


Example:
Φ40mm spherical target

Motion : 7mm in gate

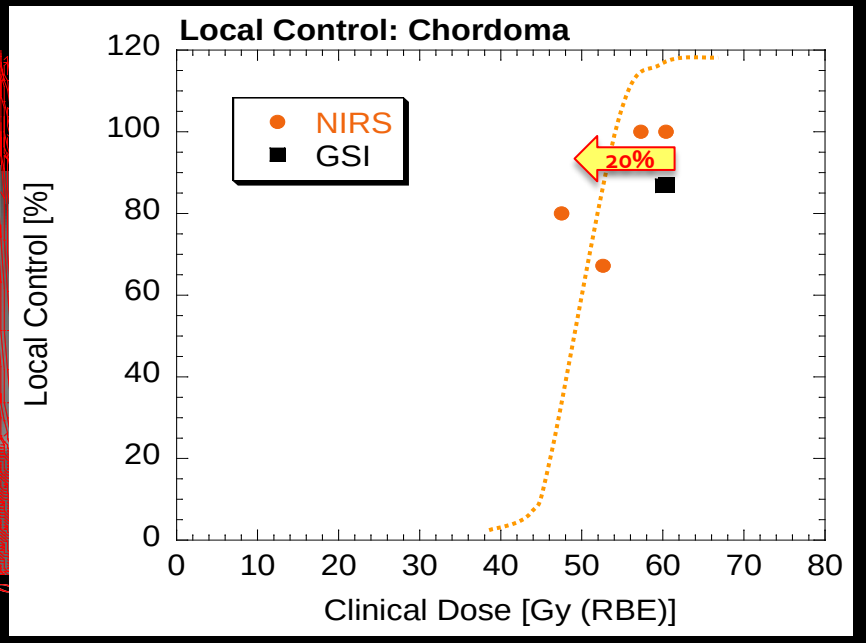
We will start treatment of a moving target with scanning beam with rescanning.

clinical dose comparison (3.3Gy (RBE) to chordoma)



Red: GSI

BW: HIMAC



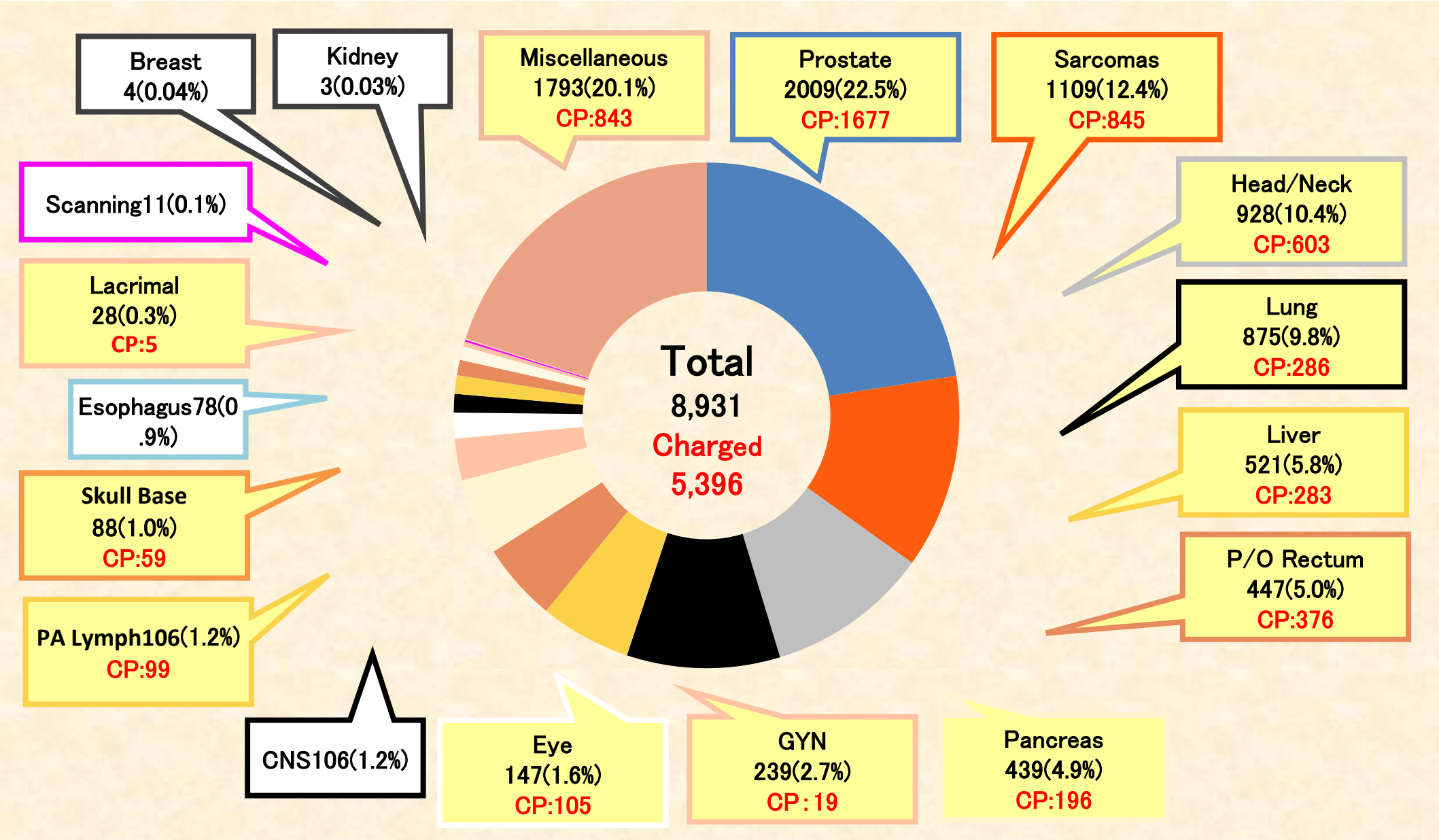
ID: CIZ251-#44 (FEB05)

Translation of NIRS dose to CNAO dose according to the difference in definition of RBE

Prescription doses (GyE) (16 fractions, 4 fractions per week)		
Indication	NIRS dose	CNAO dose
Head and neck non mesenchymal cancer	3.60	4.15 (same dose for prostate)
Skull base chordoma and chondrosarcoma	3.80	4.4 (no specific protocol for carbon ions – pt included in the sarcoma protocol and the minimum sarcoma dose is prescribed)
Head and neck non mesenchymal cancer	4.00	4.3 (salivary gland and melanoma)
Spinal chordoma and chondrosarcoma	4.20	4.6
Head and neck sarcoma	4.40	4.4 – 4.6 - 4.8 (depending on the patient)
Bone and soft tissue sarcoma	4.40	4.4 – 4.6 - 4.8 (depending on the patient)

Fossati et al : Phys Med Biol. 2012 Nov 21;57(22):7543-54.

Patient Distribution Enrolled in Carbon Therapy at NIRS (Treatment: June 1994～March 2014)



Clinical Results of C-ion RT at NIRS

- **Potential advantage of C-ion RT has been indicated in:**

  H&N ------ ACC, Adenoca, Mlanoma, Sarcoma
  Skull base and sacrum ------ Chordoma, Chondrosarcoma
  Trunk region ---------- B&S sarcoma
  Lung(NSCLC) ---------- Stage I and Locally advanced tumor
  Prostate ---------- Intermediate and high risk group
  Post-operative recurrent rectal cancer
  Pancreas cancer

  Hepatocellular cancer

  Uterine Cervix ------ Adenoca

- **Optimal fractionations or therapeutic techniques have not been confirmed yet in:**

  GBM, Bladder ca, Renal ca, etc,

- **Hypofractionation has been feasible in most tumors.**

Potential Advantage of C-ion RT

- **Dose distribution is better in both broad beam and scanning beam irradiation.**

  → Less toxicity

- **Radiobiological benefit has been confirmed to improve LC of photon-resistant tumors including:**
  - **Locally advanced large tumors**
  - **Non-squamous cell type of epitherial tumors**
  - **Sarcomas**

  → More intensive

- **Wider range of clinical indications has been demonstrated.**

  → in Sarcomas, Rectal ca, Pancreas ca

- **Hypofractionated RT has been feasible in almost all tumors.**

  → Economically more advantageous

  → More onvenient to the patients

J-CROS was established

(Japan Carbon-ion Radiation Oncology Study Group)

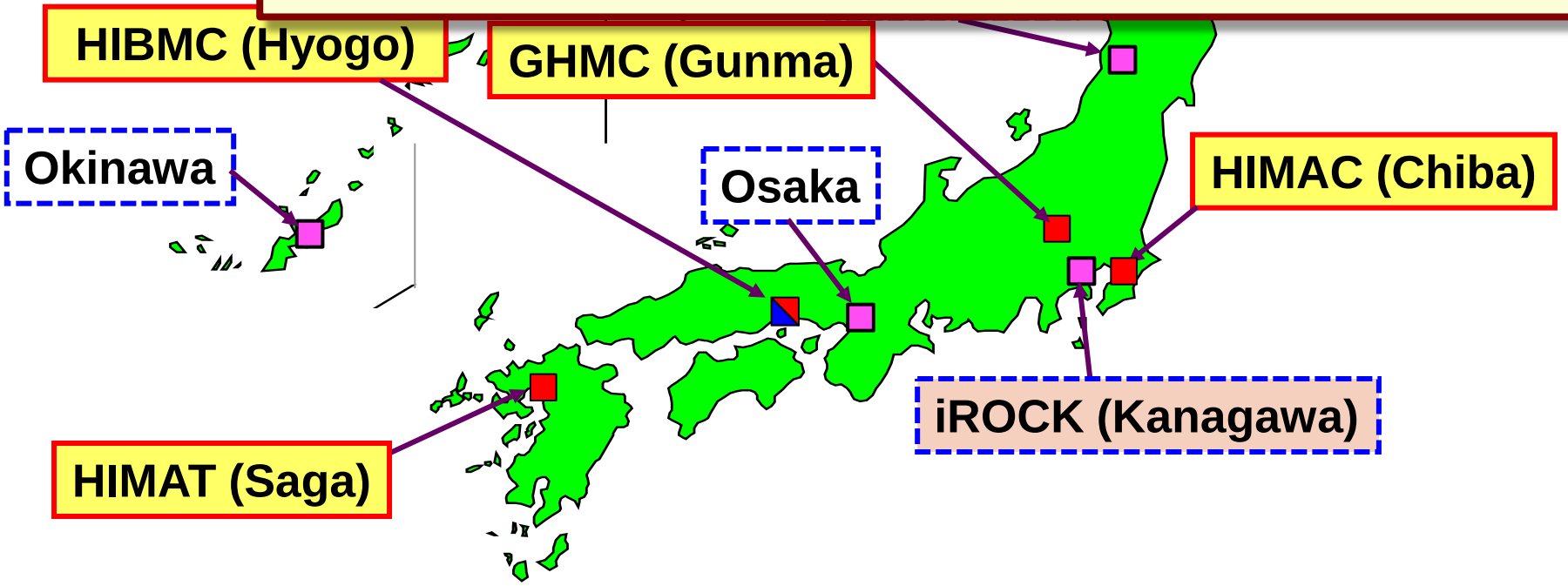
Purpose:

To Obtain a "Bench Mark Results" of C-ion RT

To Conduct Prospective Clinical Trials,

'including Phase I/II and RCT'

To Standardize C-ion RT in Various Tumors



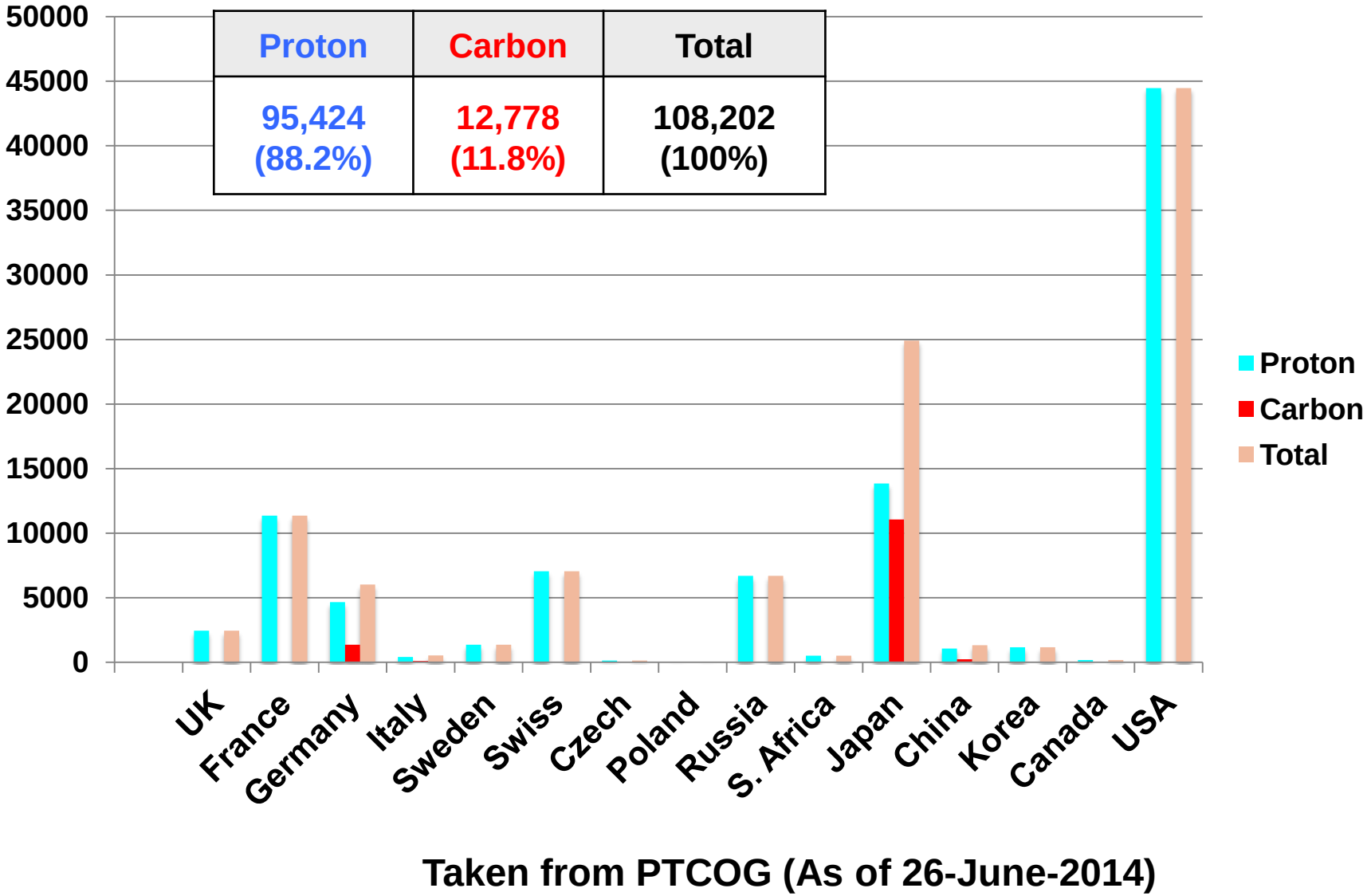
Particle therapy facilities in operation

（PTCOG Secretary, March 2014)

	Country	Proton	Carbon	Proton + Carbon	Total	
West & Central Europe	UK	1			1	12 (23.5%)
	France	2			2	
	Germany	3		1	4	
	Italy	2		1	3	
	Sweden	1			1	
	Swiss	1			1	
East Europe	Czech	1			1	2 (3.9%)
	Poland	1			1	
Russia	Russia	3			3	3 (5.9%)
Africa	S. Africa	1			1	1 (2.0%)
Asia	Japan	8	3	1	12	16 (31.4%)
	China	1	1	1	3	
	Korea	1			1	
North America	Canada	1			1	17 (33.3%)
	USA	16			16	
	Total	43	4	4	51	100%

Number of patients treated with Protons and C-ions in the world

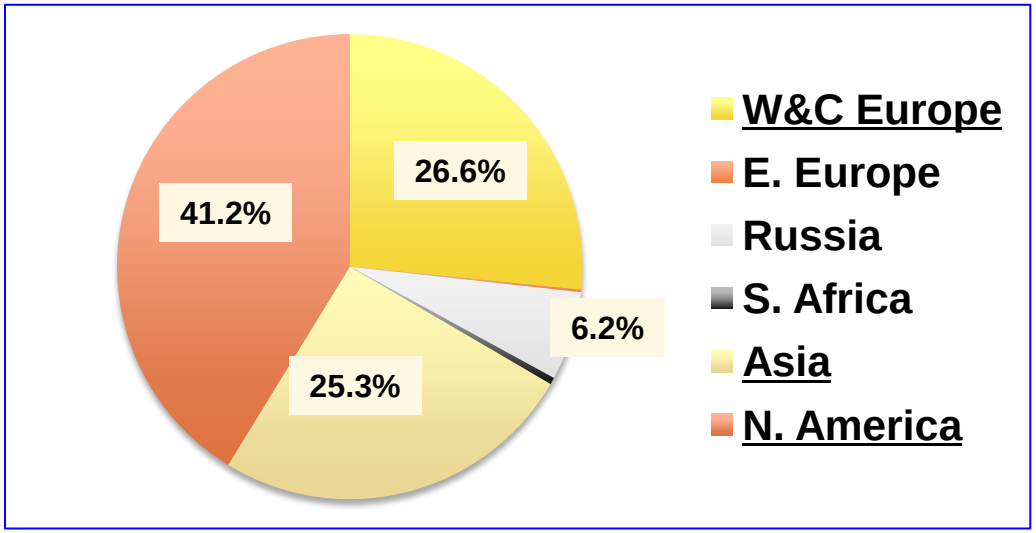
Proton	Carbon	Total
95,424 (88.2%)	12,778 (11.8%)	108,202 (100%)



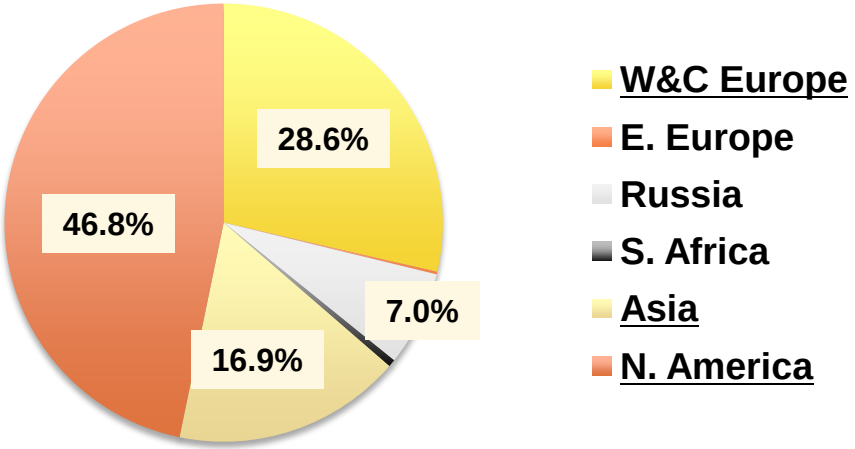
Taken from PTCOG (As of 26-June-2014)

No. of patients treated with protons and carbons in the world

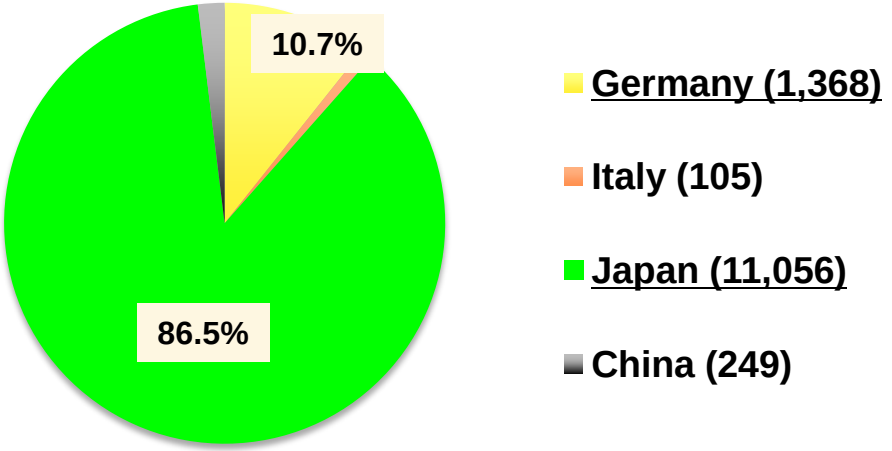
Proton and Carbon (n=108,202)



Proton (n=95,424)



Carbon (12,778)



Taken from PTCOG (As of 26-June-2014)

General considerations to be addressed

1. **What is the benefit of carbon facility?**
2. **What is the cost differential of dual modality (protons + carbon) vs. carbon alone?**
3. **Can any company deliver the system as required today?**
4. **Is the delivered system destined for rapid obsolescence?**
5. **How effective is the business model and project organization?**
6. **Is treatment planning system commercially available?**

Some considerations from clinical aspects

- **Facility and accelerator design**
  - **First or “only one” in the world, the States or Texas**
  - **Built in the most cost-effective and timely manner**
  - **C alone or Dual use?**
  - **Clinical use or clinical/research use?**
- **Rotating gantry**
  - **It is not a “must” but is strongly recommended**
  - **The biggest benefit is to reduce toxicity**
- **Irradiation method**
  - **Broad beam or scanning beam or both**
- **Motion management**
  - **Respiratory gated irradiation**
  - **Tracking method**
- **Quick way for immobilization and positioning**
- **Biological model included in the treatment planning system**

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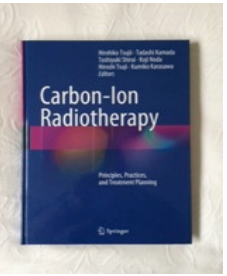

Carbon-Ion Radiotherapy

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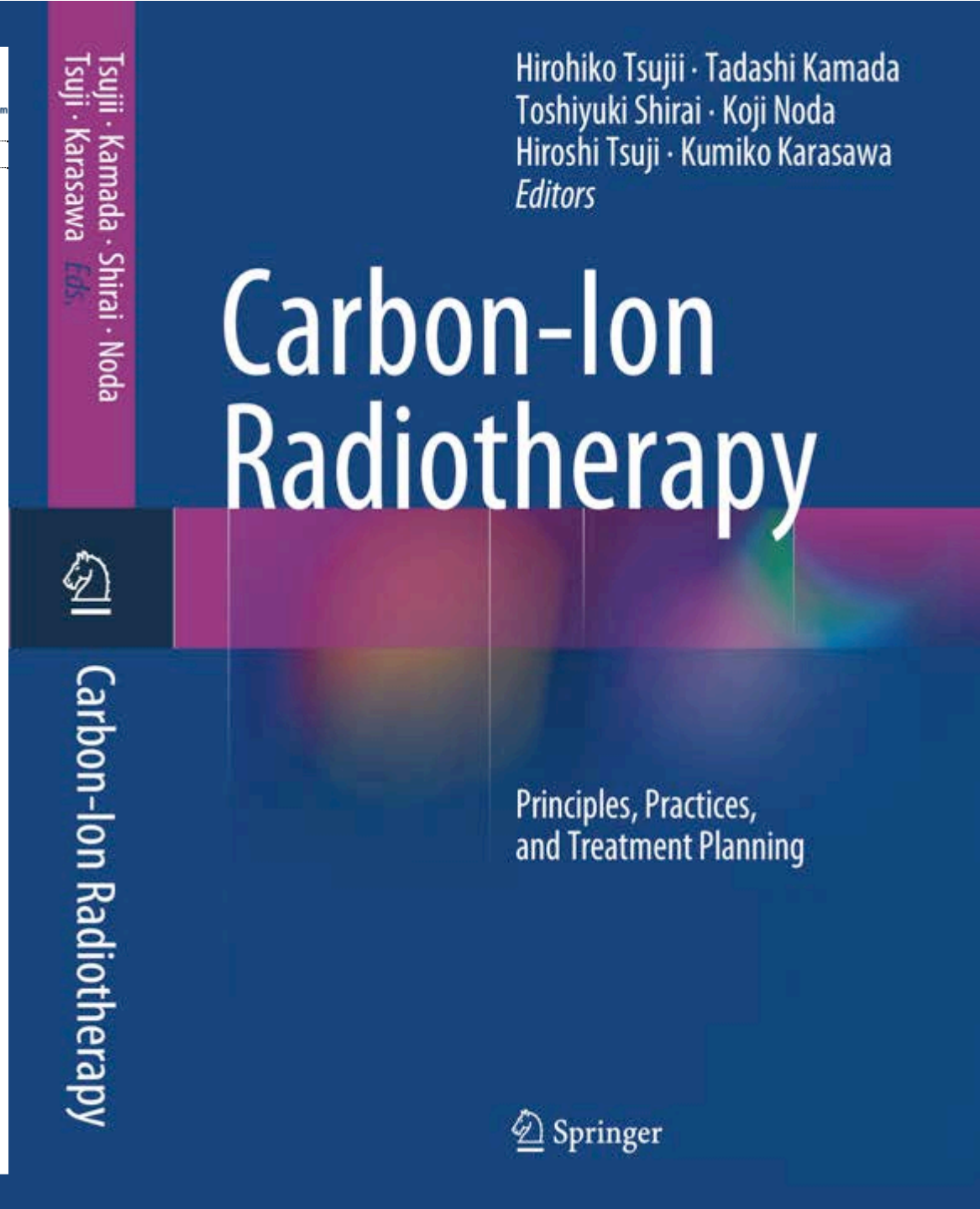
techniques and the pitfalls in treatment planning.

Readers will learn of the superior outcomes obtained with carbon-ion therapy for various types of tumors in terms of local control and toxicities. It is essential to understand that the carbon-ion beam is like a two-edged sword: unless it is used properly, it can increase the risk of severe injury to critical organs. In early series of dose-escalation studies, some patients experienced serious adverse effects such as skin ulcers, pneumonitis, intestinal ulcers, and bone necrosis, for which salvage surgery or hospitalization was required. To preclude such detrimental results, the adequacy of therapeutic techniques and dose fractionations was carefully examined in each case. In this way, significant improvements in treatment results have been achieved and major toxicities are no longer observed. With that knowledge, experts in relevant fields expand upon techniques for treatment delivery at each anatomical site, covering indications and optimal treatment planning.

With its practical focus, this book will benefit radiation oncologists, medical physicists, medical dosimetrists, radiation therapists, and senior nurses whose work involves radiation therapy, as well as medical oncologists and others who are interested in radiation therapy.

Content Level » Professional/practitioner

Keywords » Cancer radiotherapy - HIMAC - Heavy ion - Ion beams - Protons - Relative biological effectiveness



Thank You