TERA

Fondazione per Adroterapia Oncologica

SYMPOSIUM FOR UGO's 90 YEARS
CERN Council Chamber, Friday 4 April 2025

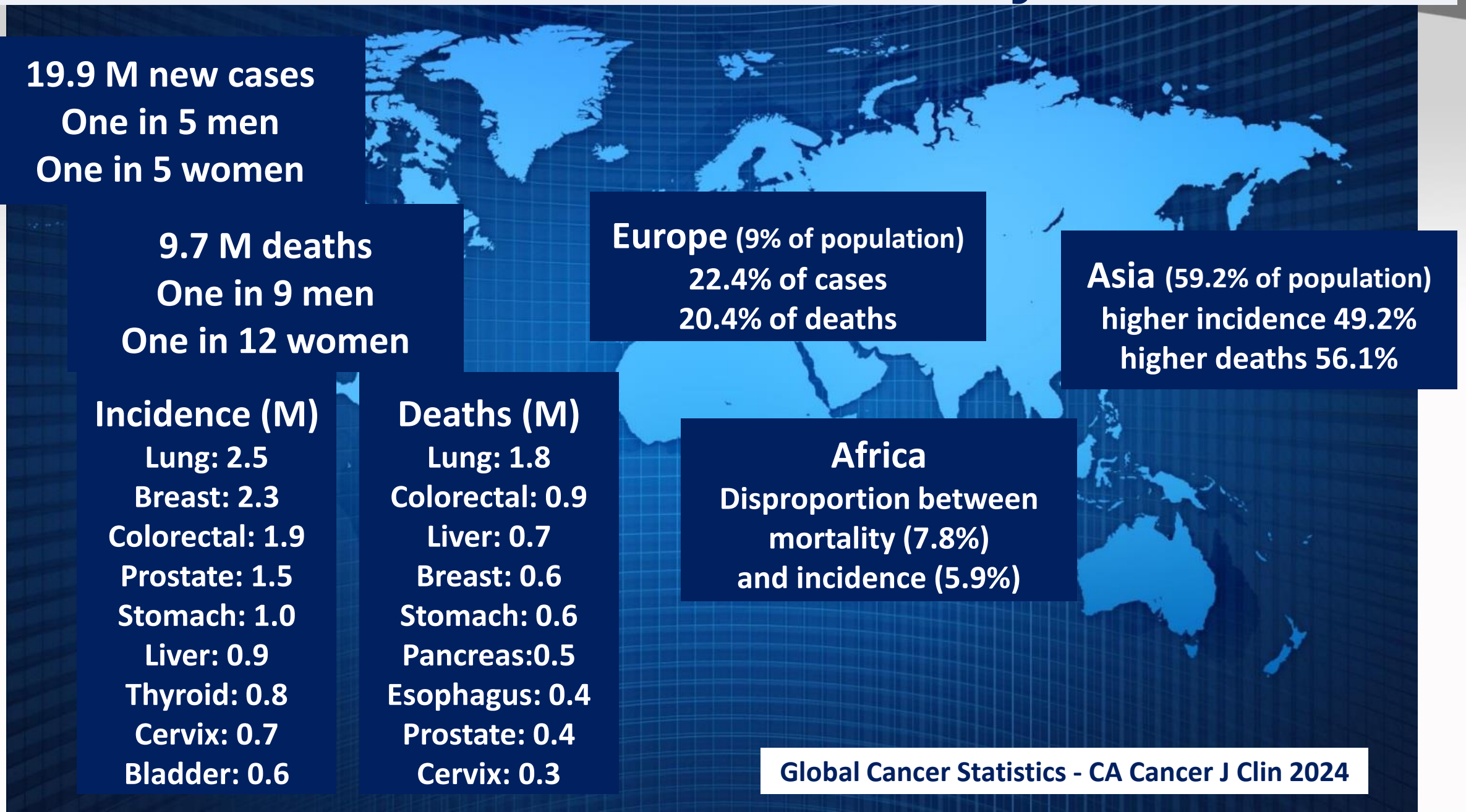
From TERA FOUNDATION to the present status of HADRON THERAPY

IEO European Institute of Oncology
CNAO

Roberto Orecchia
European Institute of Oncology & University of Milan, Milan
TERA Foundation & CNAO Foundation, Board of Directors, Novara & Pavia

A short introduction

Cancer: incidence and mortality worldwide



19.9 M new cases
One in 5 men
One in 5 women

9.7 M deaths
One in 9 men
One in 12 women

Europe (9% of population)
22.4% of cases
20.4% of deaths

Asia (59.2% of population)
higher incidence 49.2%
higher deaths 56.1%

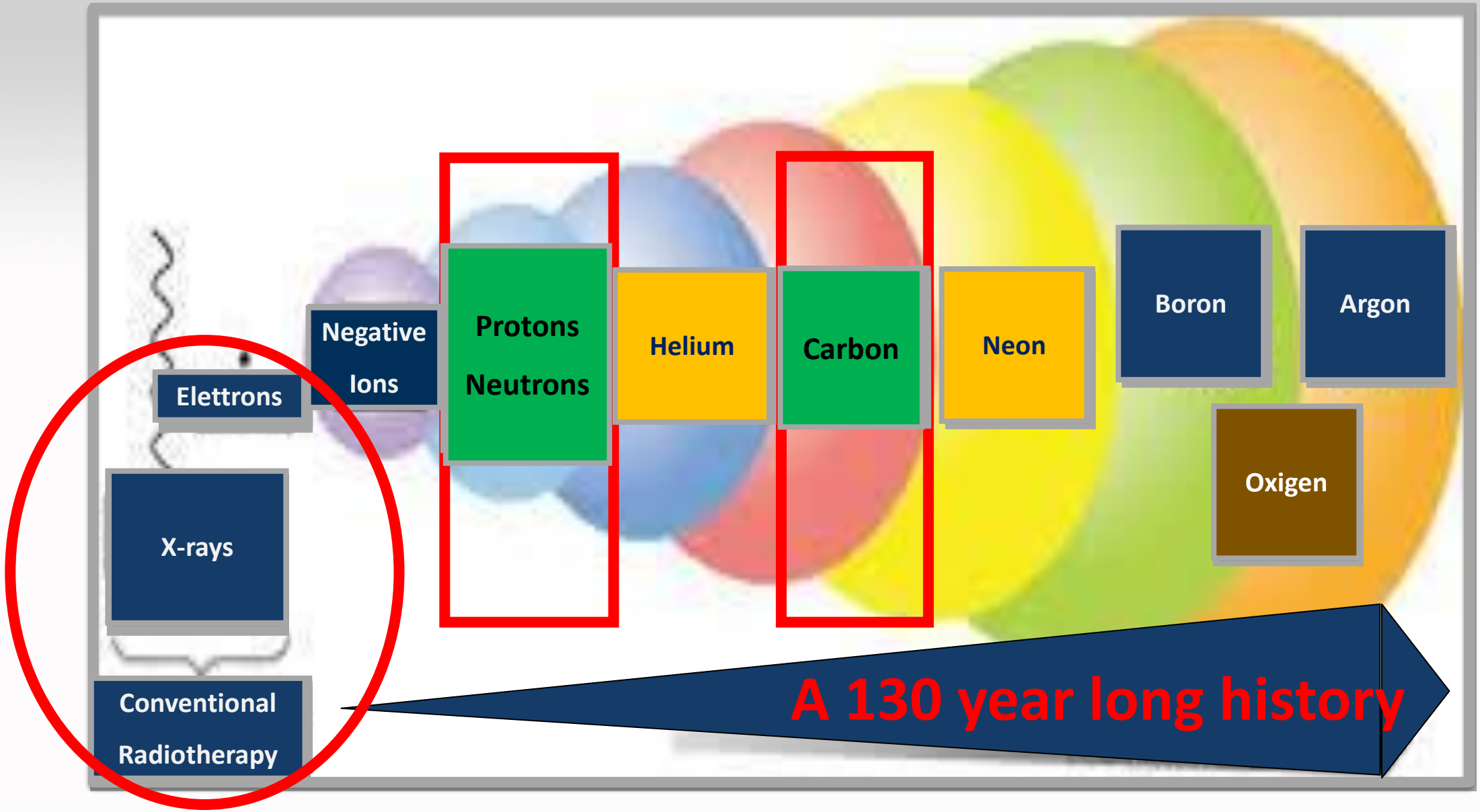
Africa
Disproportion between mortality (7.8%) and incidence (5.9%)

Incidence (M)
Lung: 2.5
Breast: 2.3
Colorectal: 1.9
Prostate: 1.5
Stomach: 1.0
Liver: 0.9
Thyroid: 0.8
Cervix: 0.7
Bladder: 0.6

Deaths (M)
Lung: 1.8
Colorectal: 0.9
Liver: 0.7
Breast: 0.6
Stomach: 0.6
Pancreas:0.5
Esophagus: 0.4
Prostate: 0.4
Cervix: 0.3

Global Cancer Statistics - CA Cancer J Clin 2024

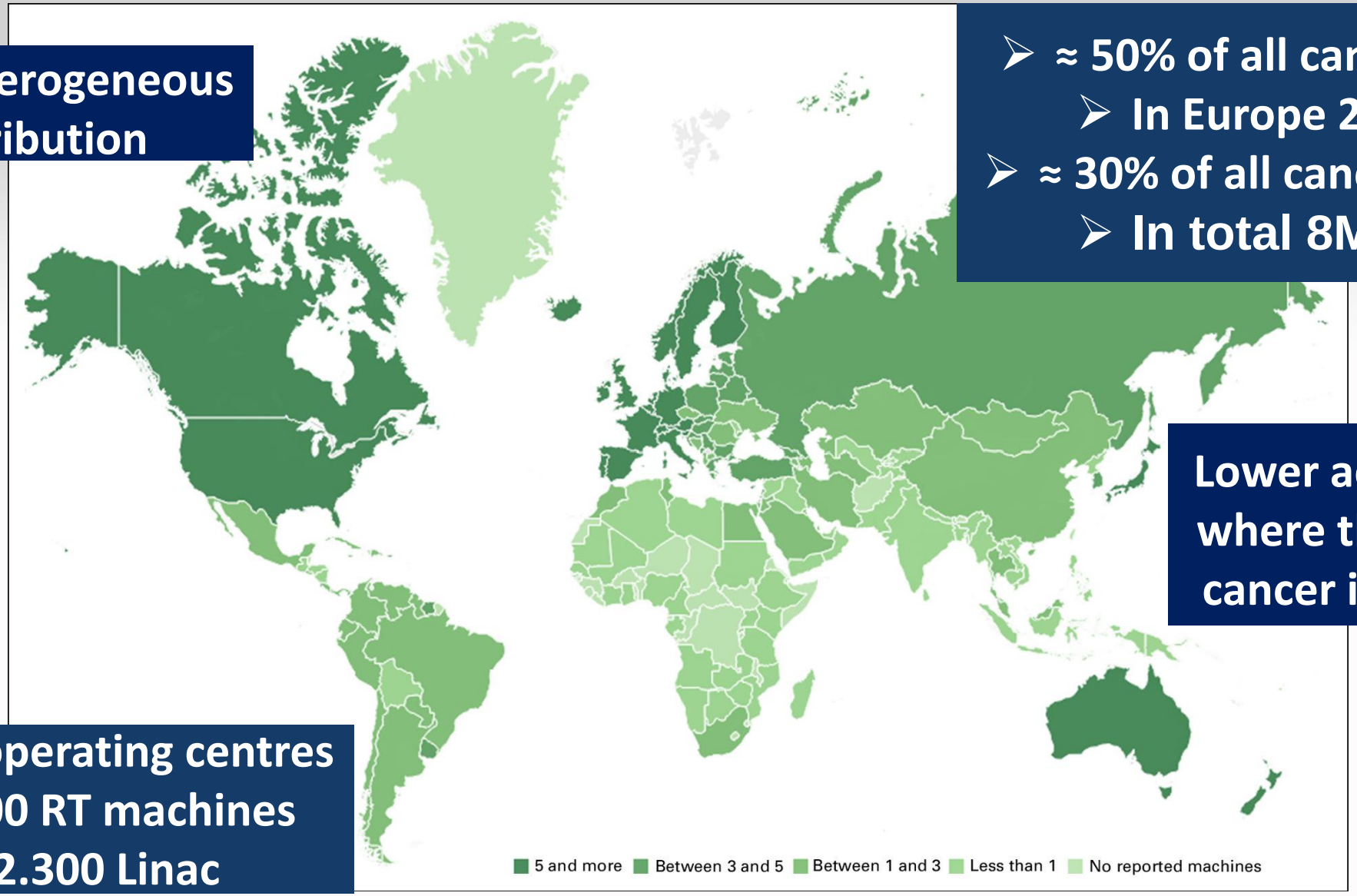
RT: from X-rays to photons to heavier ions



Access to radiotherapy per million population

Very heterogeneous distribution

- ≈ 50% of all cancers in HICs
- In Europe 2M cases
- ≈ 30% of all cancers in LMICs
- In total 8M cases



Lower access in LMICs, where the incidence of cancer is higher (67%)

- 7.500 operating centres
- 14.500 RT machines
- 12.300 Linac

JCO Global Oncol 2021

Before TERA … …

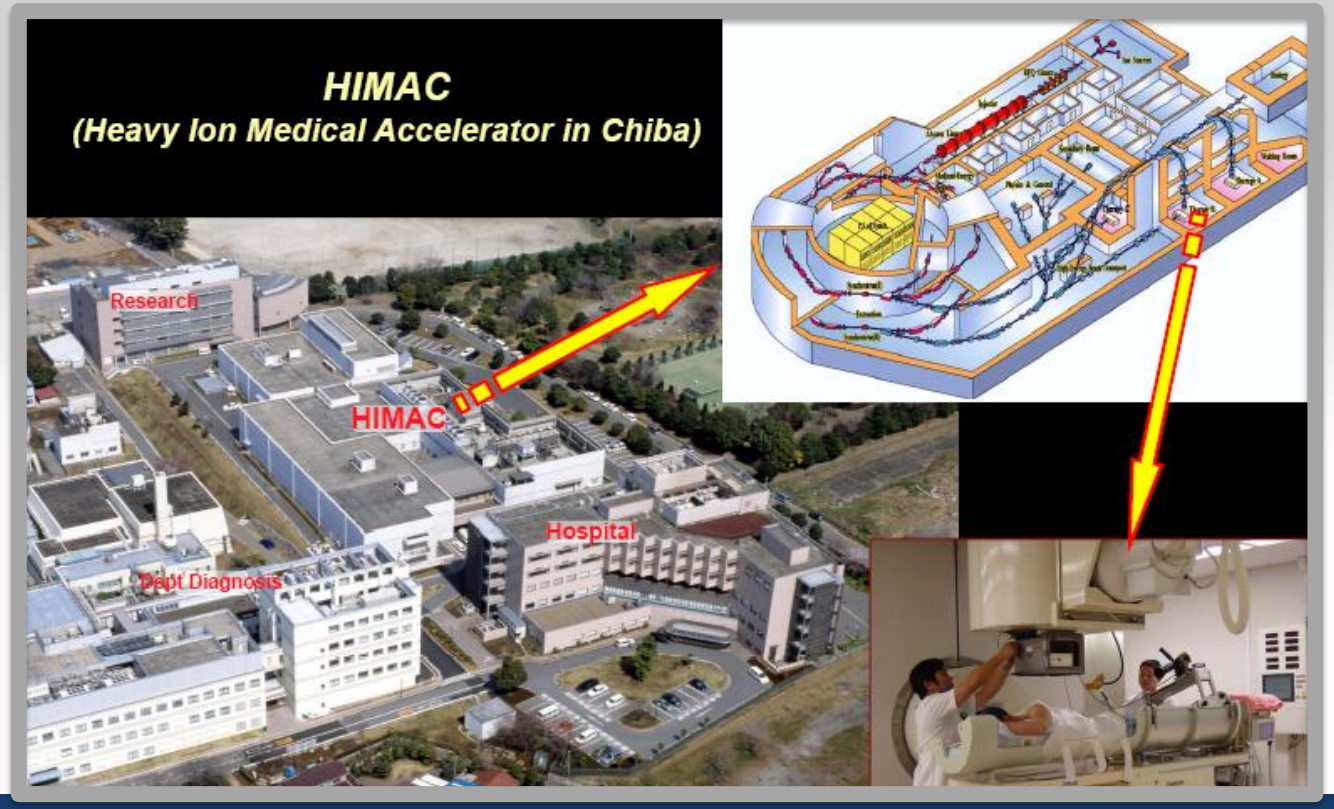
Neutron beams

- 1938: first patients at Berkeley (24 patients, single fraction)
- 1939-43: fractionated dose (202 patients)
- 1965-82: first randomized trials in London, Edinburgh, Clatterbridge, Seattle, Houston, and Chicago
- 1992: 16.000 patients in 23 neutron therapy facilities worldwide (5 in USA, 5 in Germany, 3 in Russia, 2 in Japan and France, one in UK, Belgium, Korea, China, Saudi Arabia, and South Africa)
- 1951-92: first clinical trials on BNCT in USA and Japan

First Ions in clinics

- 1975: first patients at Bevalac, Berkeley, even ion properties were well know since the early ‘50
- 2000 patients with helium and 500 with neon in 20 years (skull base, H&N, sarcoma, prostate, eye melanoma, glioma, biliary tract, …)

First hospital-based Carbon Ion Radiotherapy



- 1988: construction of HIMAC (accelerator & building)
- 1994: first patients with carbon ions at NIRS
- >15,000 patients up to date

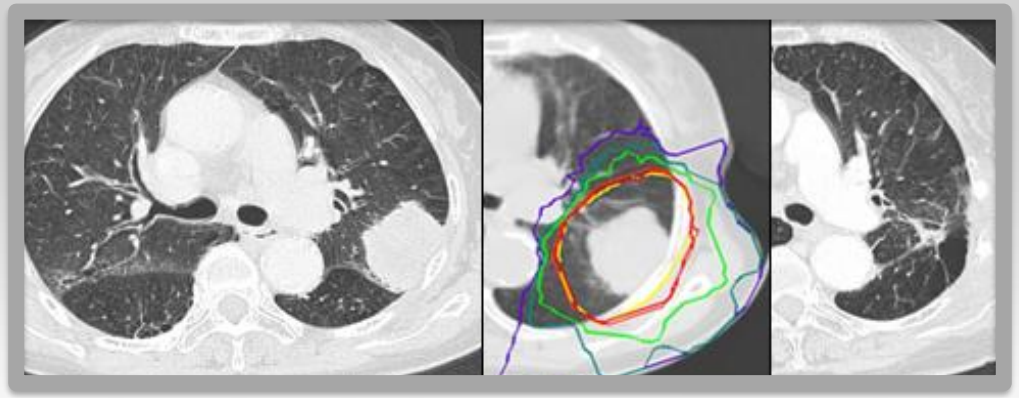
QST Hospital
National Institutes for Quantum and Radiological Science and Technology

NIRS: where CIRT started …

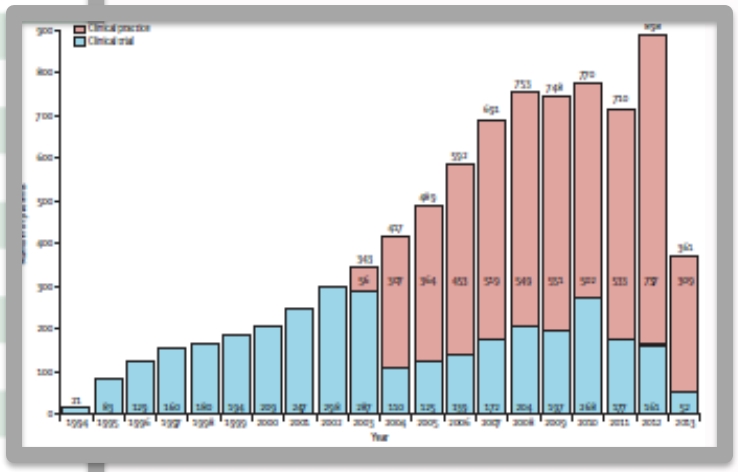
Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience

Lancet Oncol 2015

Tadashi Kamada, Hirohiko Tsujii, Eleanor A Blakely, Jürgen Debus, Wilfried De Neve, Marco Durante, Oliver Jäkel, Ramona Mayer, Roberto Orecchia, Richard Pötter, Stanislav Vatnitsky, William T Chu



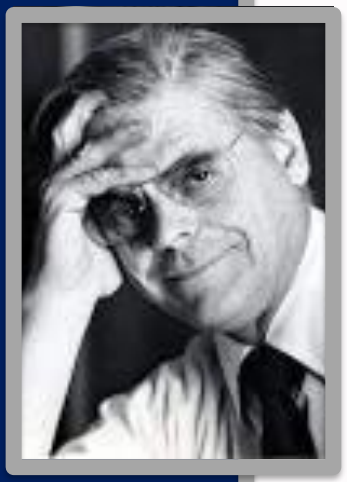
	Total number of patients (%)	Clinical practice
Prostate	1731 (22%)	1399
Bone and soft tissue	1033 (13%)	780
Head and neck	854 (11%)	529
Lung	795 (10%)	207
Liver	485 (6%)	250
Post-operative rectum	408 (5%)	338
Pancreas	353 (4%)	113
Gynaecological	207 (3%)	10
Eye	128 (2%)	86
CNS	106 (1%)	0
Para aortic lymph node	94 (1%)	87
Skull base	85 (1%)	56
Oesophagus	71 (1%)	0
Lacrimal gland	24 (<1%)	1
Scanning	11 (<1%)	0
Miscellaneous	1547 (20%)	715



Benefits in non-SCC of the H&N (adenocarcinoma, ACC, melanoma and sarcoma)
Long-term improvement in LC of chordomas (skull base and sacrum)
Biological advantage in radioresistant tumors (bone and soft tissue sarcomas)
Results comparable to surgery in pelvic recurrence of rectal cancer
In pancreatic cancer combination with CT improved OS and LC
Hypofractionation: single-fraction for early-stage NSCLC, 2-fractions for HCC and 16- or 12-fractions for prostate cancer

Protons

- Proposed by Robert Wilson in 1946
- 1954-74: ≈1,000 pituitary glands and tumours, at Berkeley
- 1957: first patients in Uppsala
- 1961: first patients in Boston (HCL & MGH)
- Years ’70: first patients in Russia and Japan
- 1990: the first clinical centre at Loma Linda University

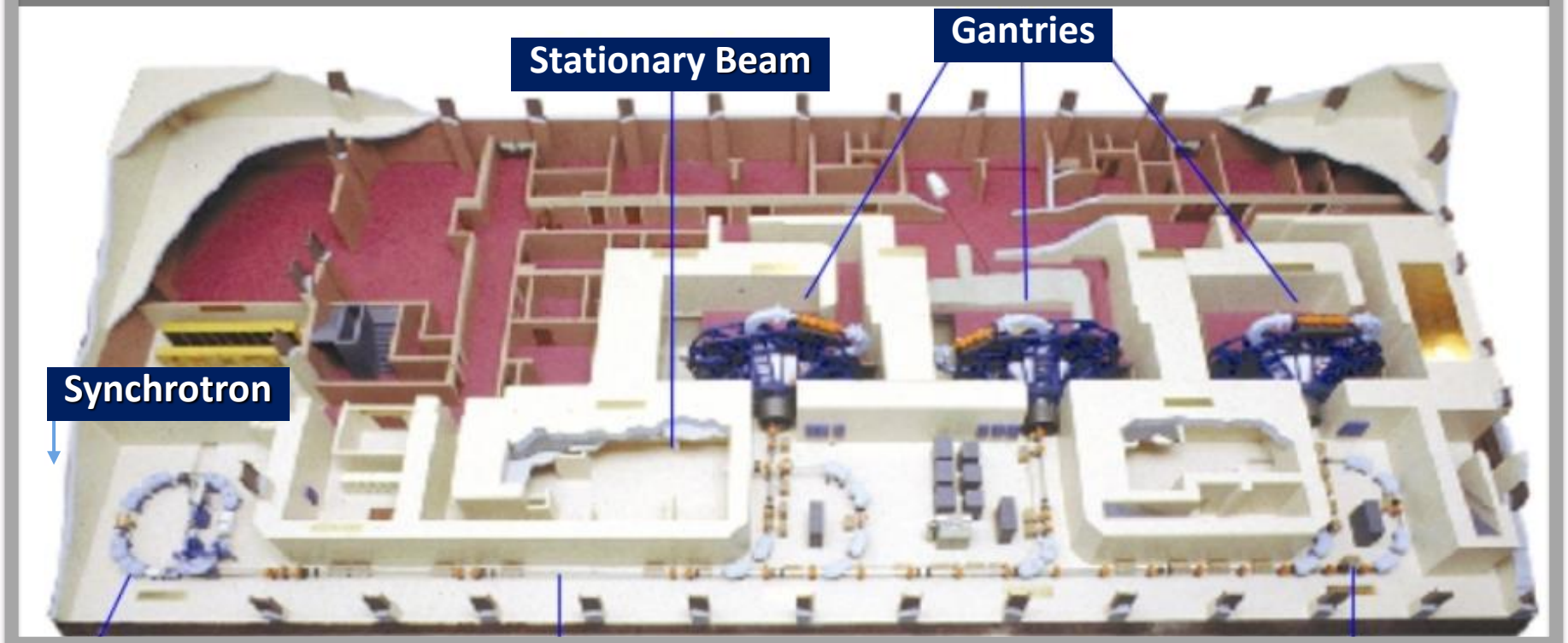


First hospital-based Proton Therapy centre

First patient: 1992

23.460+ Patients Treated

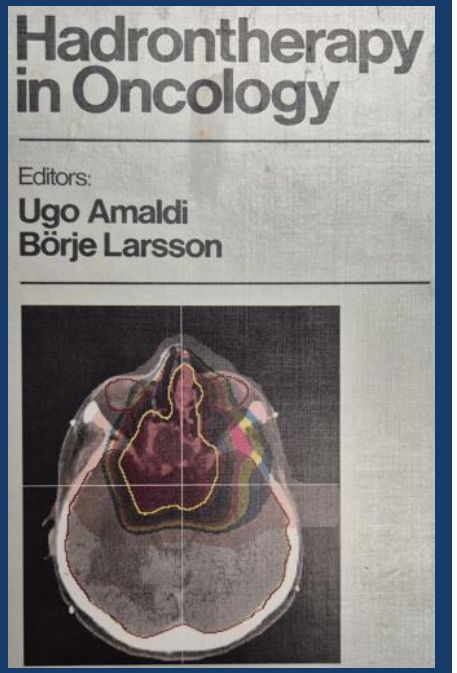
14.821+ Prostate Patients Treated



The role of TERA in developing Hadron Therapy

The TERA Foundation

- U. Amaldi & G. Tosi, “For a Centre of Teletherapy with Hadrons”, 1991
- 15 September 1992: TERA (Therapy with Hadronic Radiation) Foundation was established in Novara, Italy
- 1992: the idea of an Italian Hadron Therapy began to take shape
- 1993: First International Conference on Hadron Therapy in Como



Umberto Veronesi

Believe in science means believe in the future

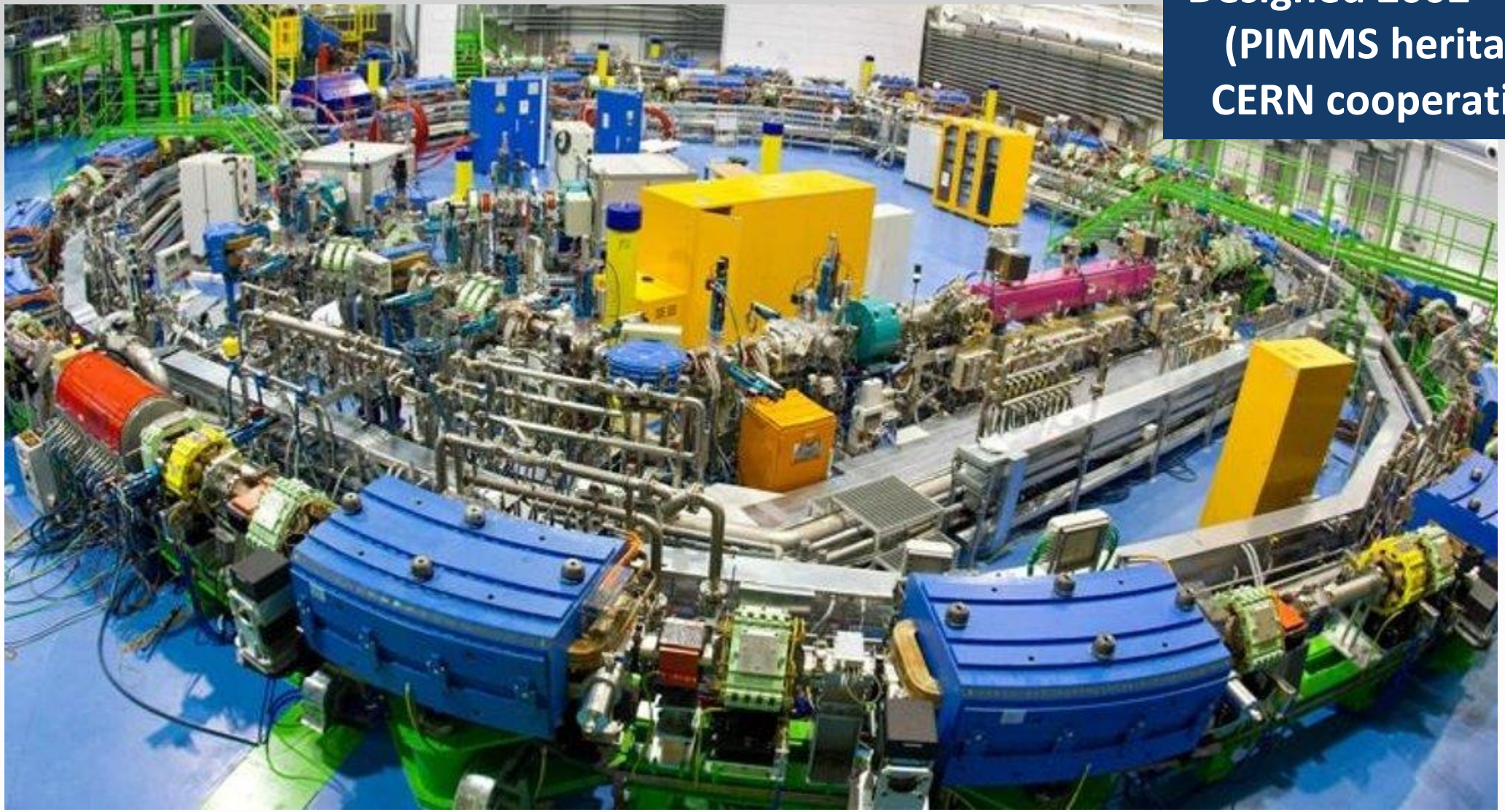
Establishment of the CNAO foundation by the Ministry of Health (law decree n.388; 23/12/2000)

30 years of history of TERA

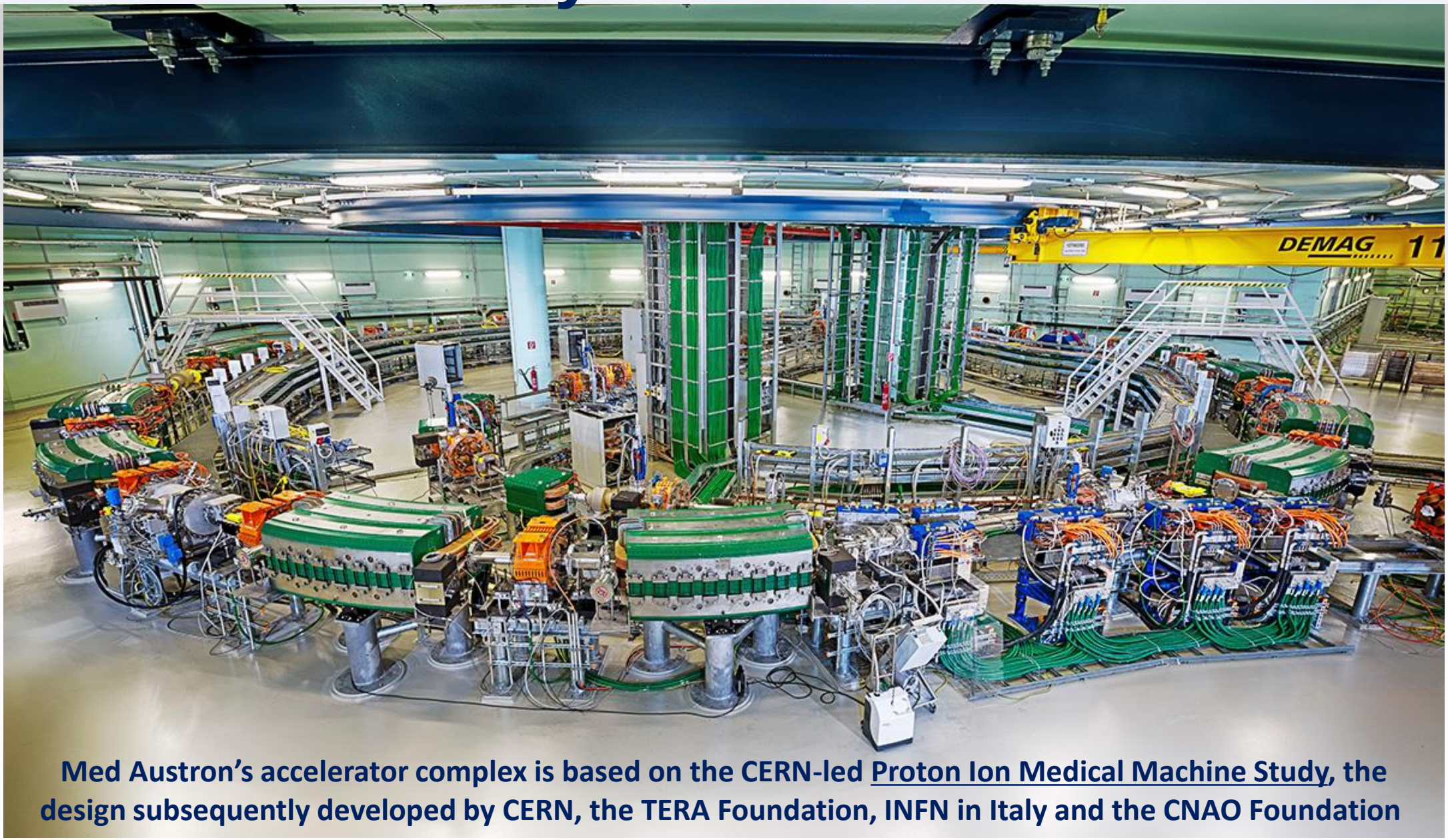
- The initial group has become “TERA Collaboration” (>120 people)
- CNAO (National Centre for Oncological Hadron Therapy) was the main activity until 2000 (… … transferred people)
- Projects and Committees: Compact accelerator, Pathologies and Treatments, Radiobiology, Dosimetry and Microdosimetry, ….
- >200 TERA Reports, 5 books: green, blue, red, white (and silver)
- Funding fellowships and salaries for over 15 young engineers and physicists (≈30M€)

CNAO: a success story

Designed 2002 - 2003 (PIMMS heritage, CERN cooperation)



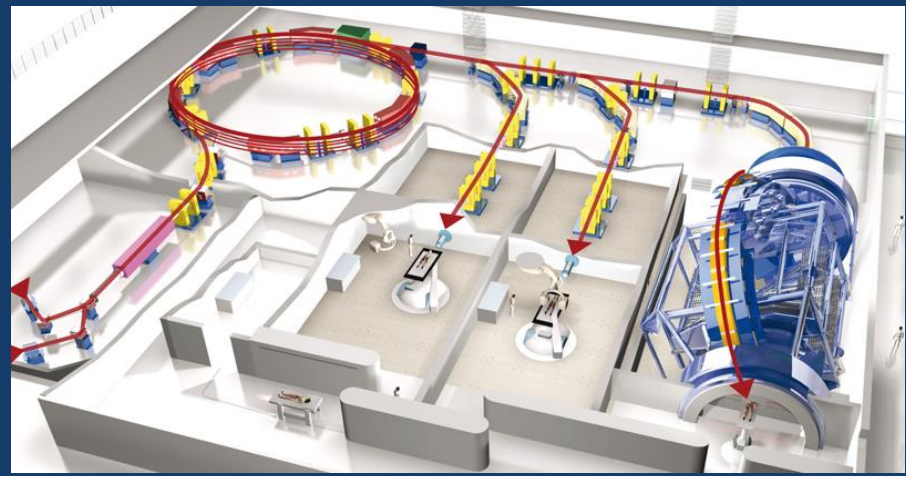
2019: Austrian synchrotron debuts CIRT



Med Austron's accelerator complex is based on the CERN-led Proton Ion Medical Machine Study, the design subsequently developed by CERN, the TERA Foundation, INFN in Italy and the CNAO Foundation

The GSI-Heidelberg Project

- 1993: GSI project to built a high-tech heavy ion facility
- 1997: the first 2 patients with brain tumor treated
- 1998: second treatment block at GSI
- 2003: approval for University Medical Centre Heidelberg
- 2005: building completed
- 2009: treatment started



Hadron Therapy today

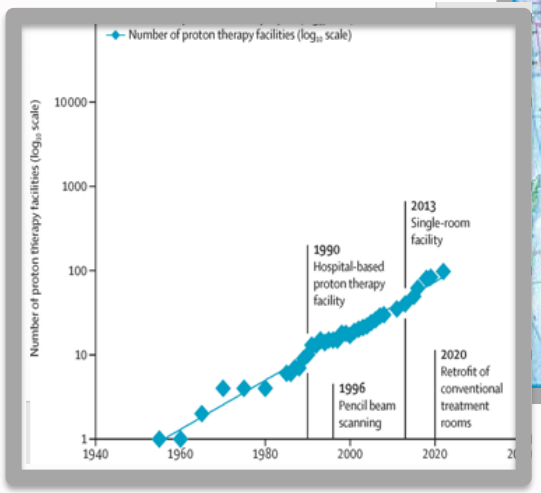
Hadron Therapy centres worldwide

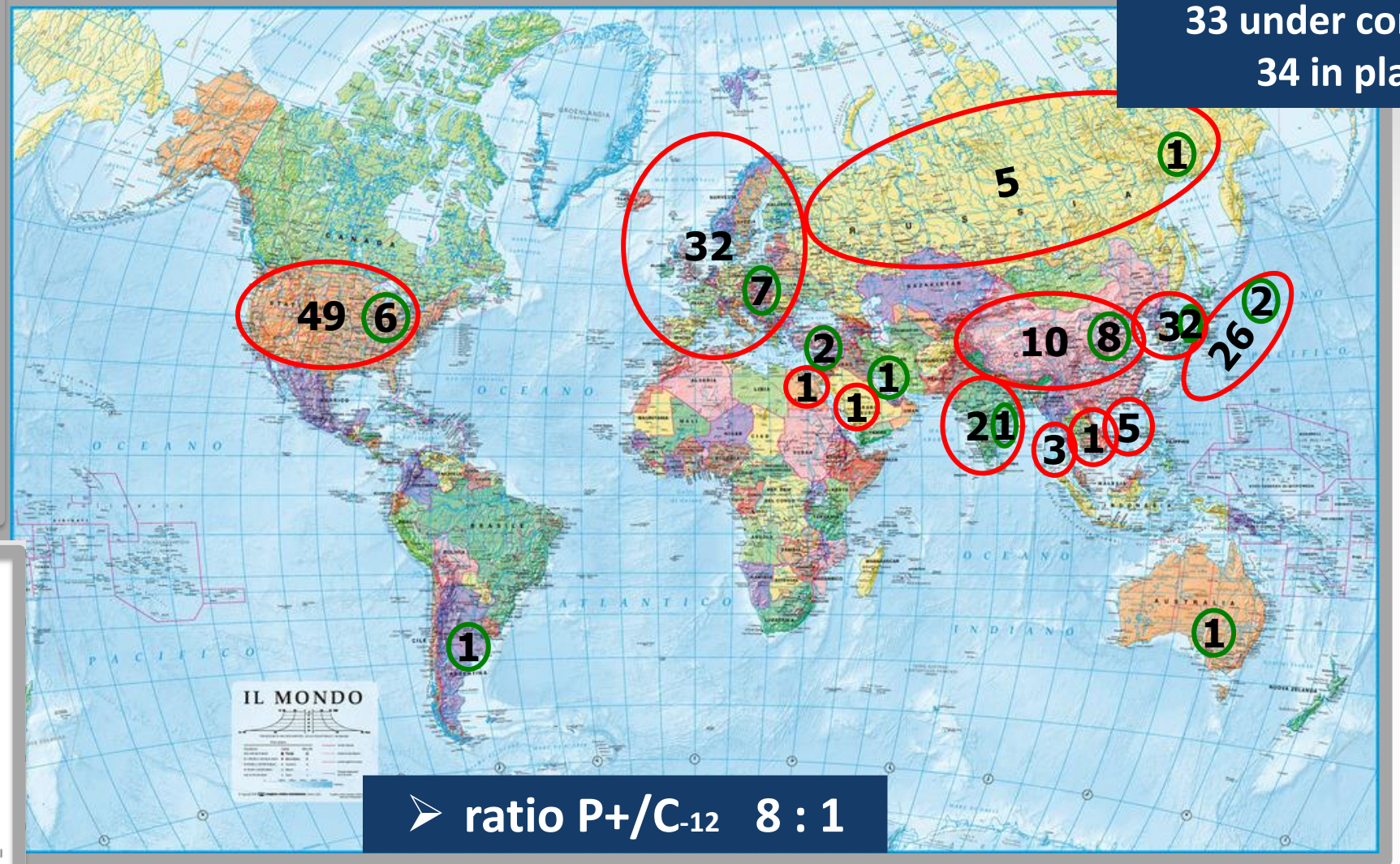
In operation

Under construction

*16 with Carbon Ion

3 under construction



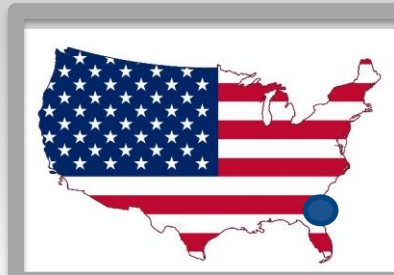


140* operating centers
33 under construction
34 in planning

➢ ratio P+/C_{-12} 8 : 1

Yan S et Al. Lancet Oncol 2023; PTCOG Website, March 2025

Carbon Ion centres worldwide



Mayo, Jacksonville

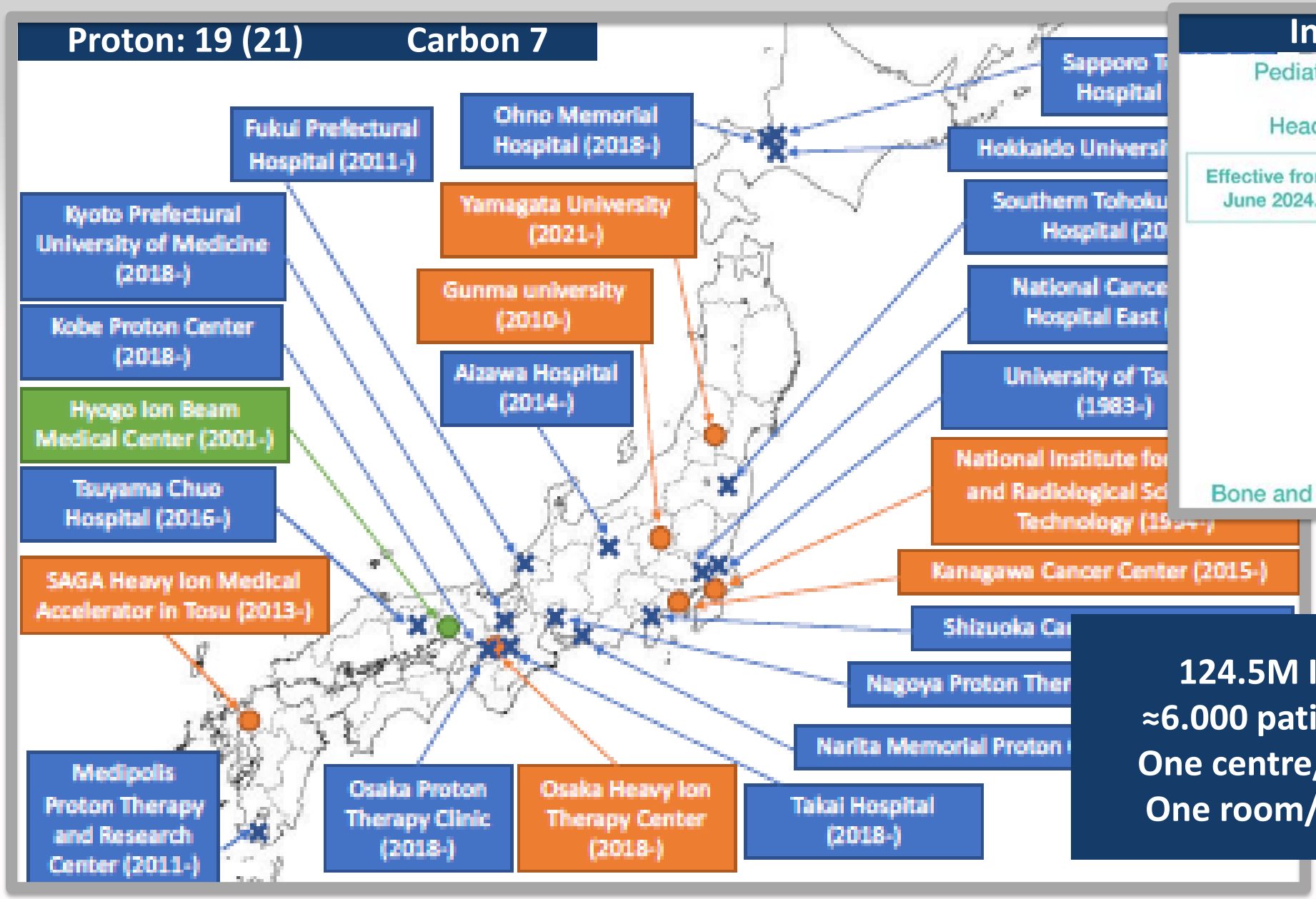
PARALLEL OPPOSED EDITORIAL

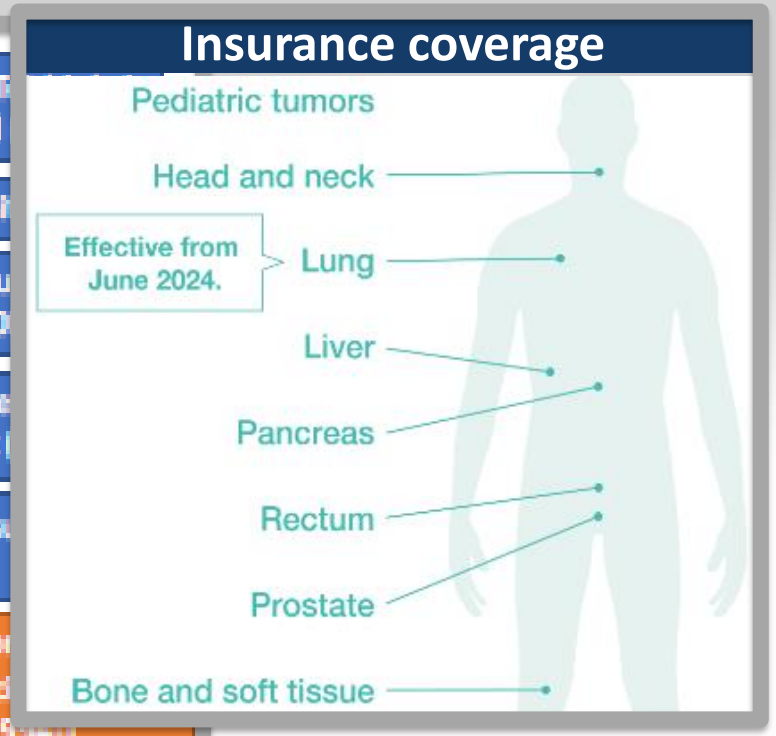
We are ready for clinical implementation of Carbon Ion Radiotherapy in the United States

J Appl Clin Med Phys 2020; 21:12:6–9

PTCOG Website, March 2025

Japan: a unique situation





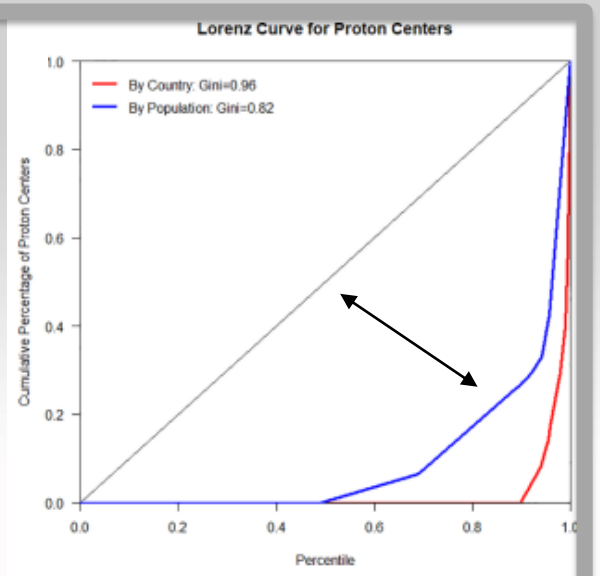
124.5M Inhabitants
≈6.000 patients per year
One centre/4.8M people
One room/2.0M people

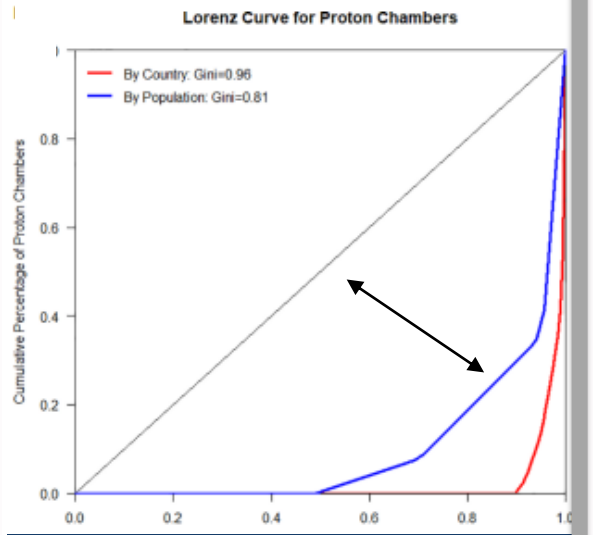
Access of patients to Hadron Therapy

Extremely high difference between HICs/LMICs

Only 21% of HICs had PT centers

Average patients volume is stable





The curves very far from the diagonal line

Persistent key gap area in access in LMICs where there is an alarming increase in incidence

Estimated percentage of patients
1.5% in UK, 10% in Netherlands, 14.5% in France, 15% in Sweden, and 16% in Italy

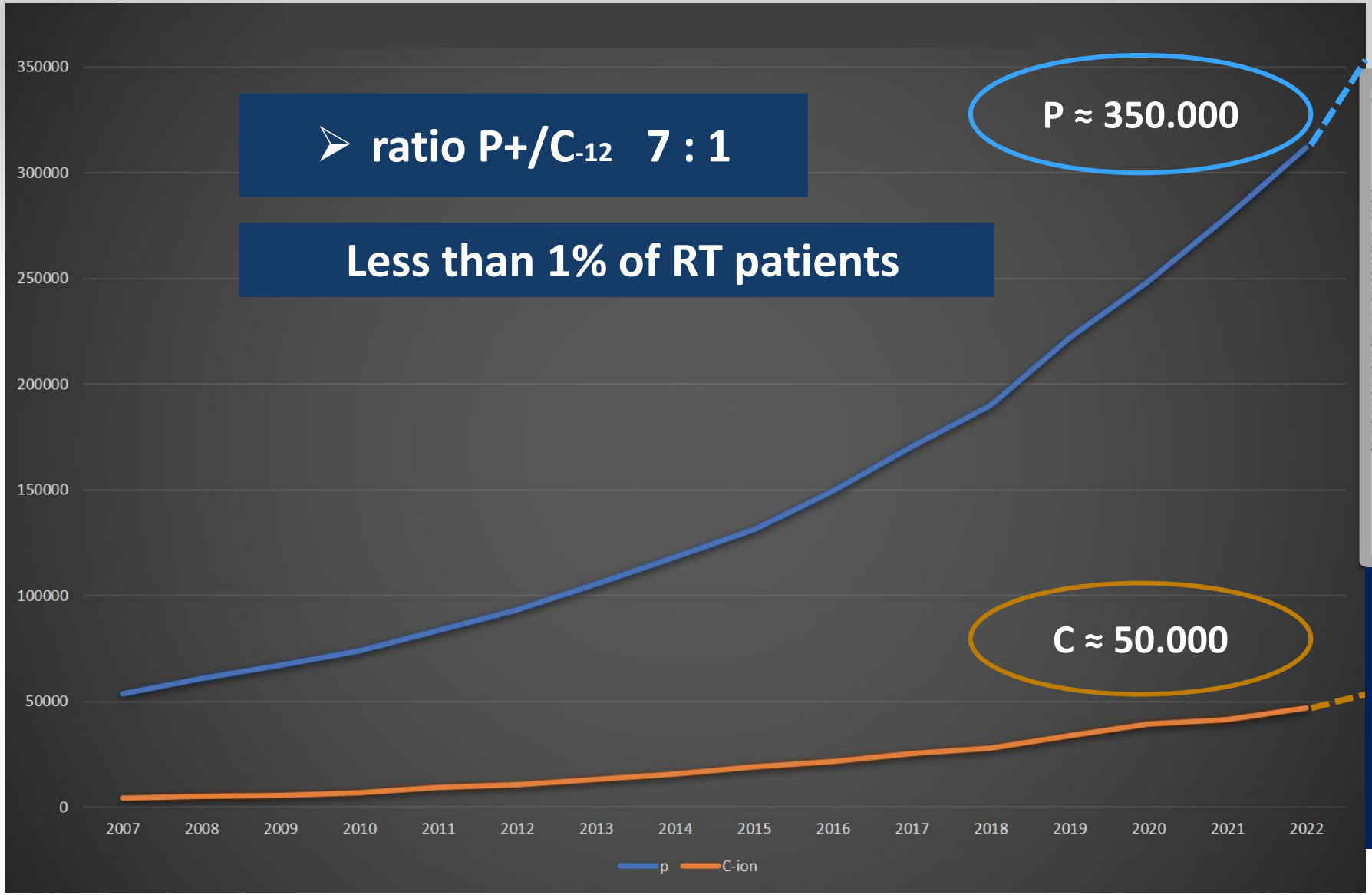
Dutch Model: 1/3 of H&N cancers

In LMICs the estimated percentage of PT patients varies from at least 1.0% (conservative) up to 7.5% (generous). This means at least 12 centers in India

In LMICs 80% of pediatric medulloblastoma (PMB)
In US PT for PMB increased 10-fold in 15 years
PT more cost-effective, with a long-term gain of 0.68 quality-adjusted life-years (QALY) per child

Xia Z et A. Front Oncol 2022

Patients treated since 2007

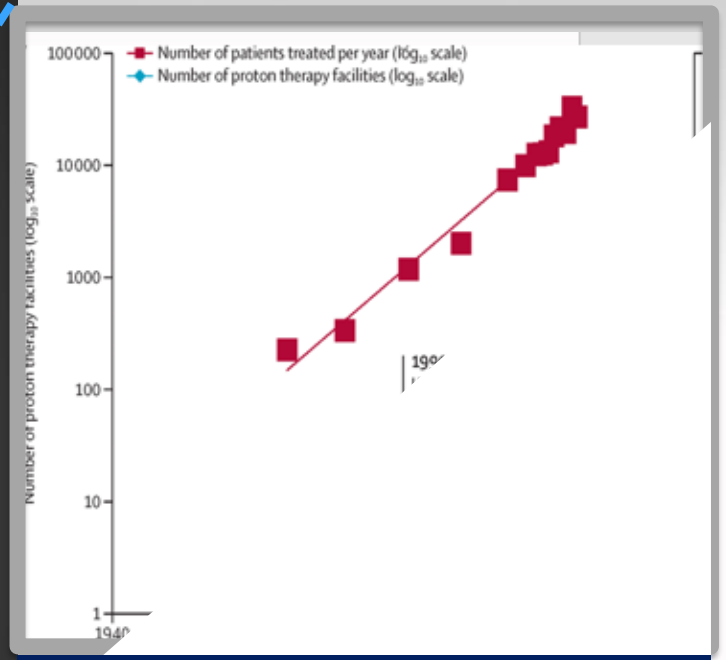


➢ ratio P+/C_{-12} 7 : 1

Less than 1% of RT patients

P ≈ 350.000

C ≈ 50.000



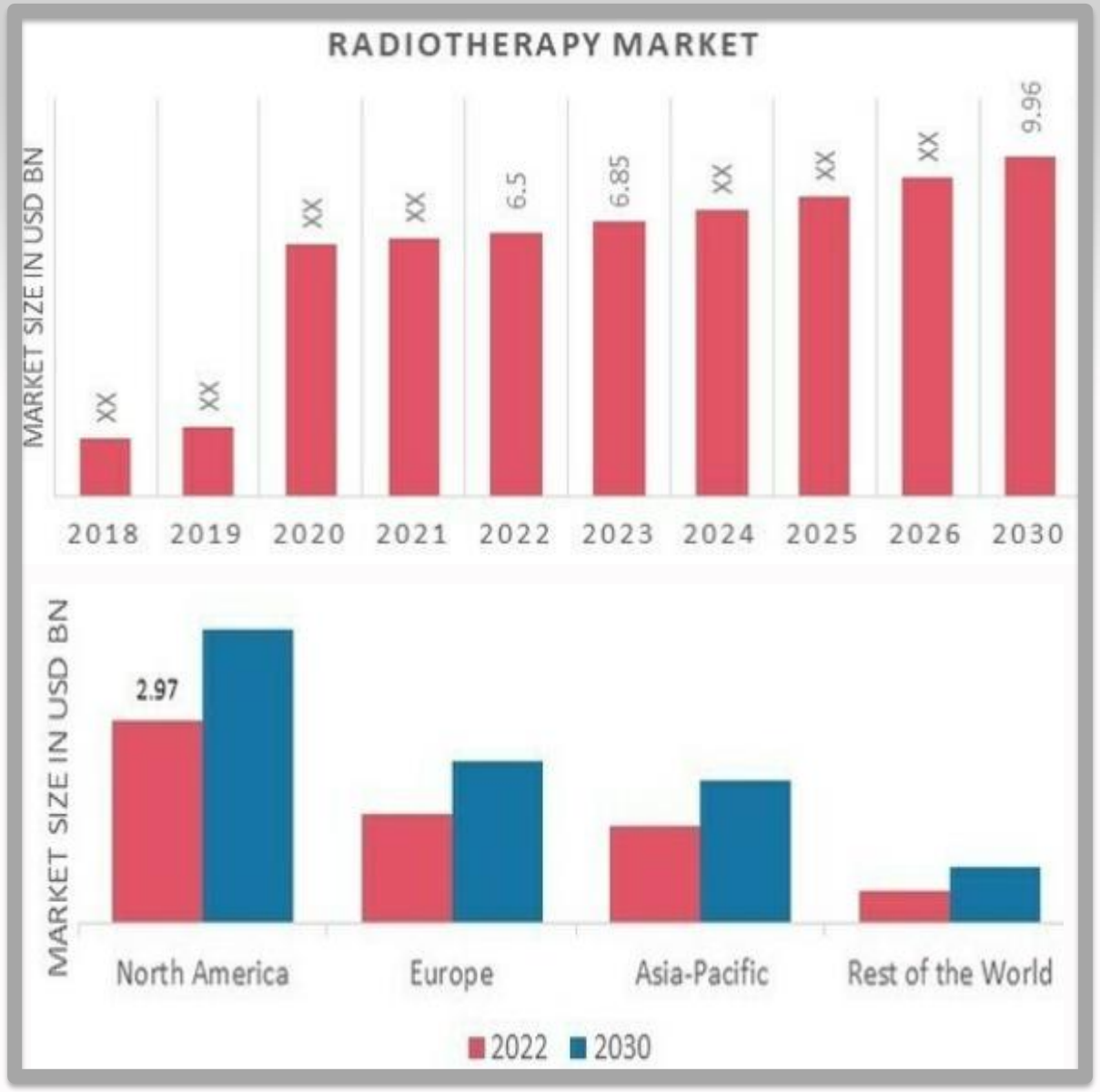
Between 2007 and 2017
from ≈52.000 to >170.000

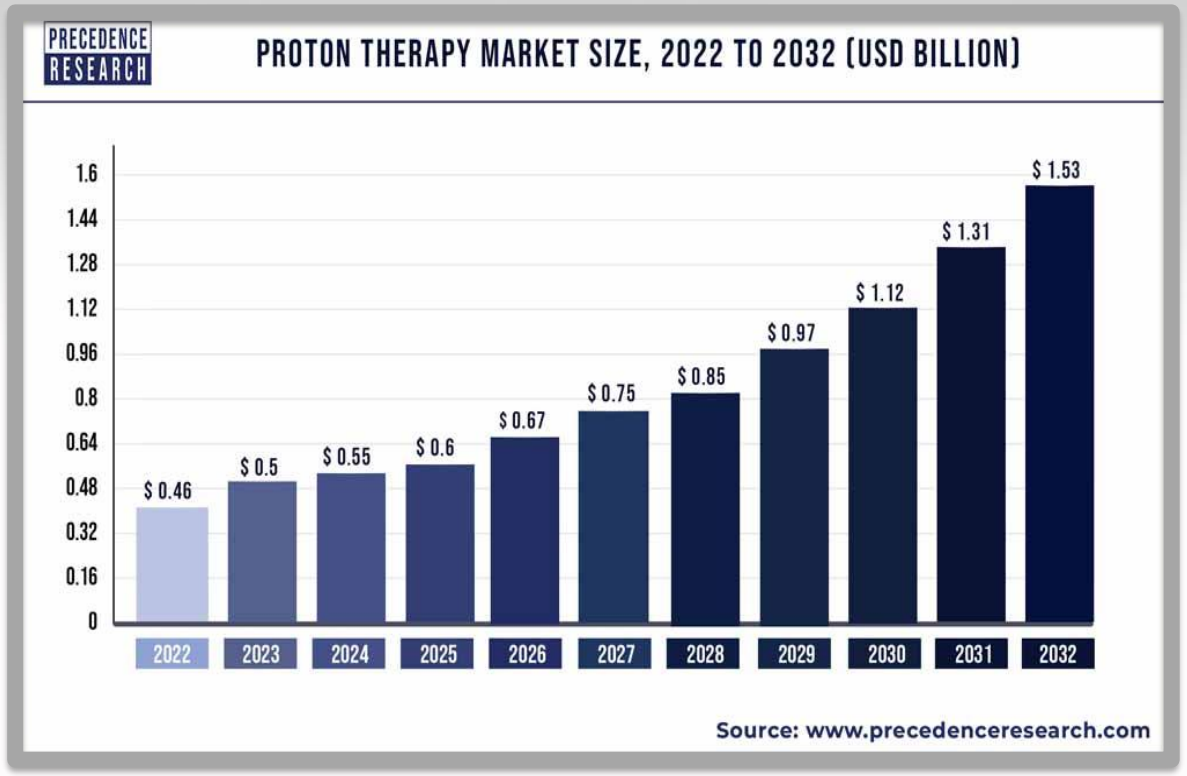
In the last five years
up to 350.000
(>25.000 new patients/year)

Yan S et Al. Lancet Oncol 2023; PTCOG Website, March 2025

What in future?

Market growth





MARKET RESEARCH FUTURE®

Collaboration and Networking

- ENLIGHT
- ULICE
- INSPIRE
- EU Integrating Activity HITRIplus
- ESTRO-EPTN
- PTCOG
- PTCOG-NA

Improvement of patient care

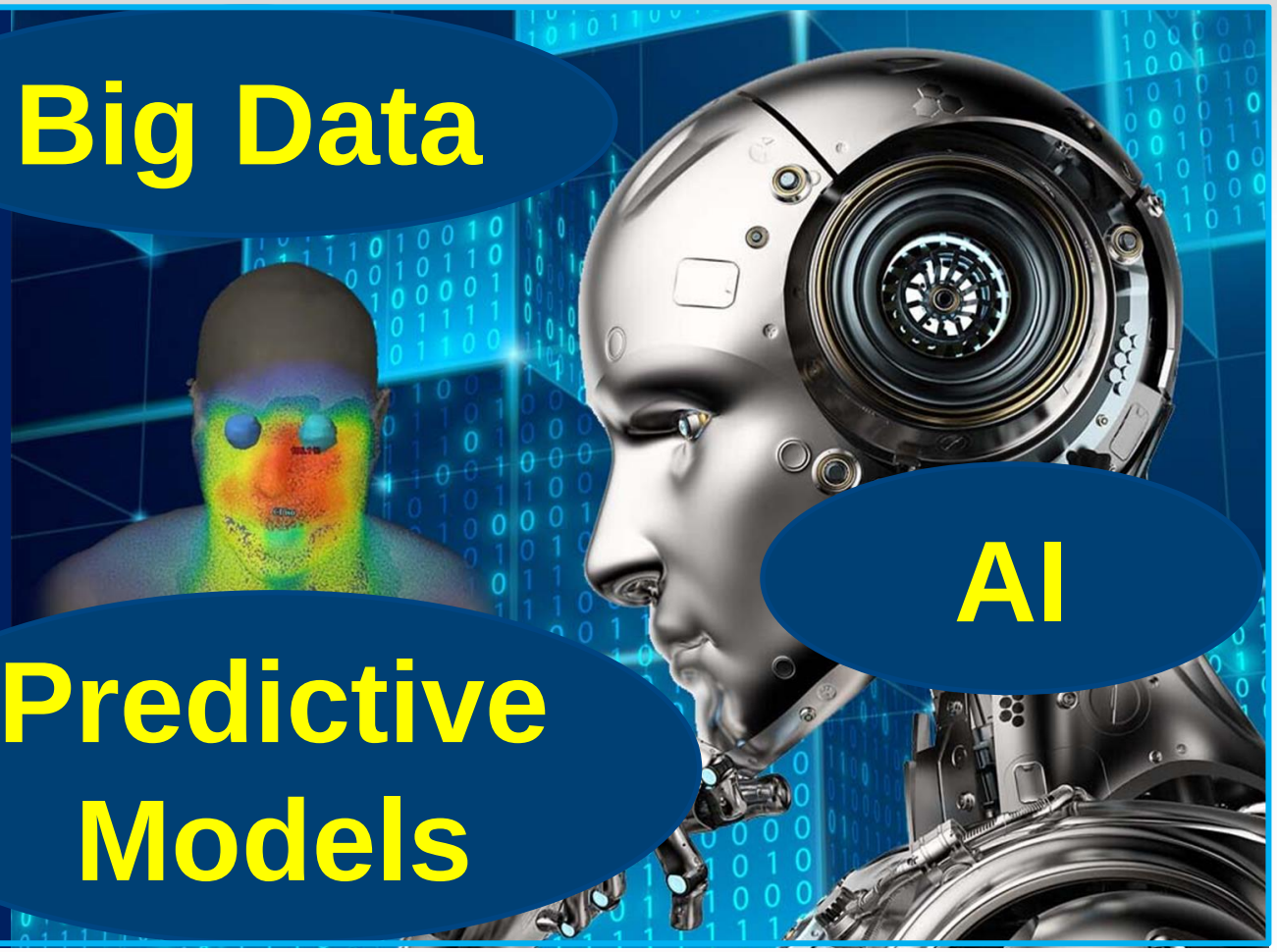
- Evidence Based Data
- Combined treatment
- Treatment planning optimization (plan quality)
- In-room Image-guided
- Online adaptive therapy
- Intra-fraction and inter-fractions motion control
- Full 4D beam delivery

Ensure equitable access to patients

- Reduced cost and size
- Infrastructure availability
- Automatic self-diagnostic and self-calibration
- Regulatory body and insurance coverage
- Hypofractionation
- Education and training
- Engagement of different stakeholders

Precision Radiation Oncology

- Genomics
- Proteomics
- Metabolomics
- Immunomics
- Epigenomics
- ……..
- Radiomics
- Radiogenomics
- Dosiomics



Thank You so much !!!!!!

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