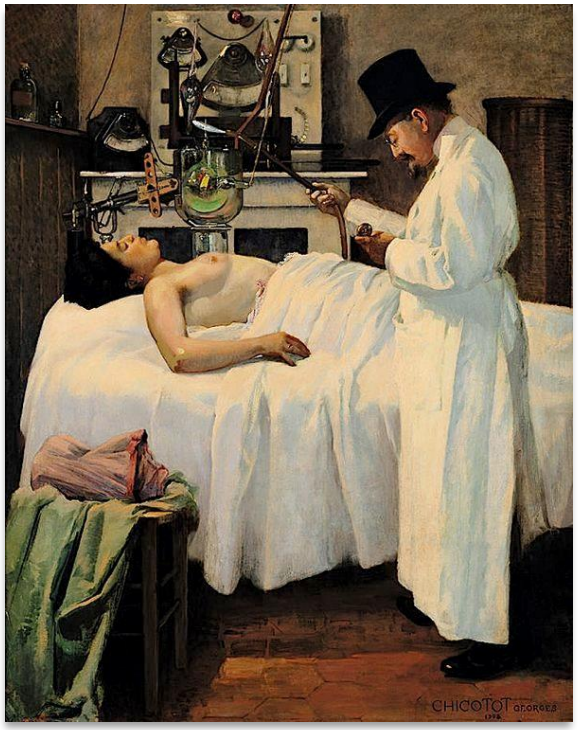
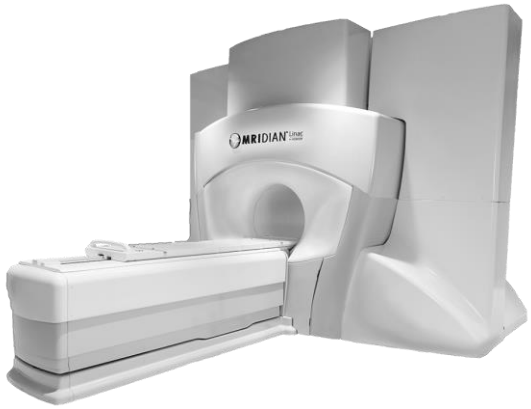
Proton therapy: Present evidence and future

Cai Grau,
Aarhus, Denmark

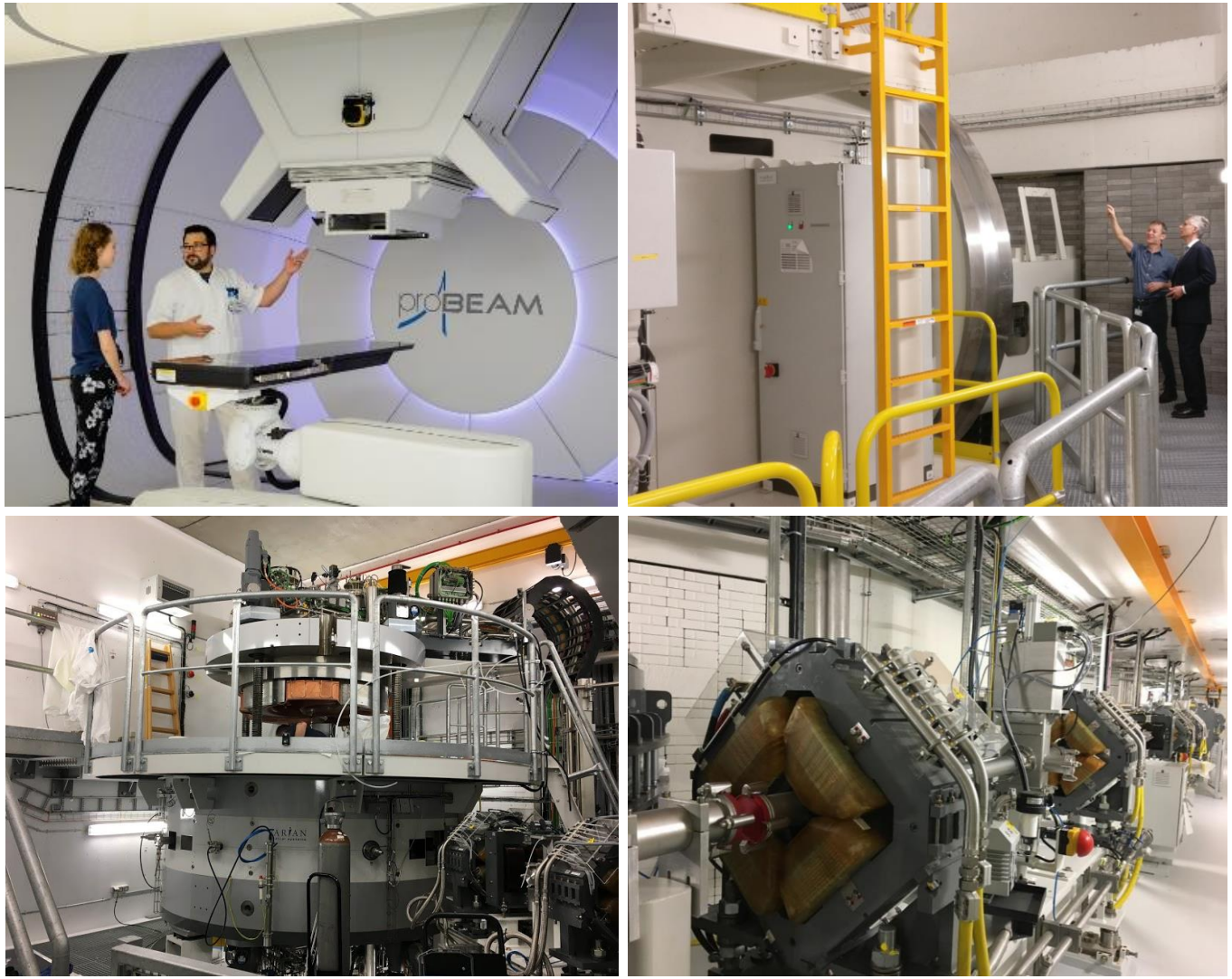
DCPT

Technical innovations in radiation oncology





Ion beam therapy – particle therapy – protons



Aarhus University Hospital, 2020

- Large construction, gantries weighing 100+ tons
- Heavy upfront investment, €100-200M
- The most expensive piece of equipment in health care?

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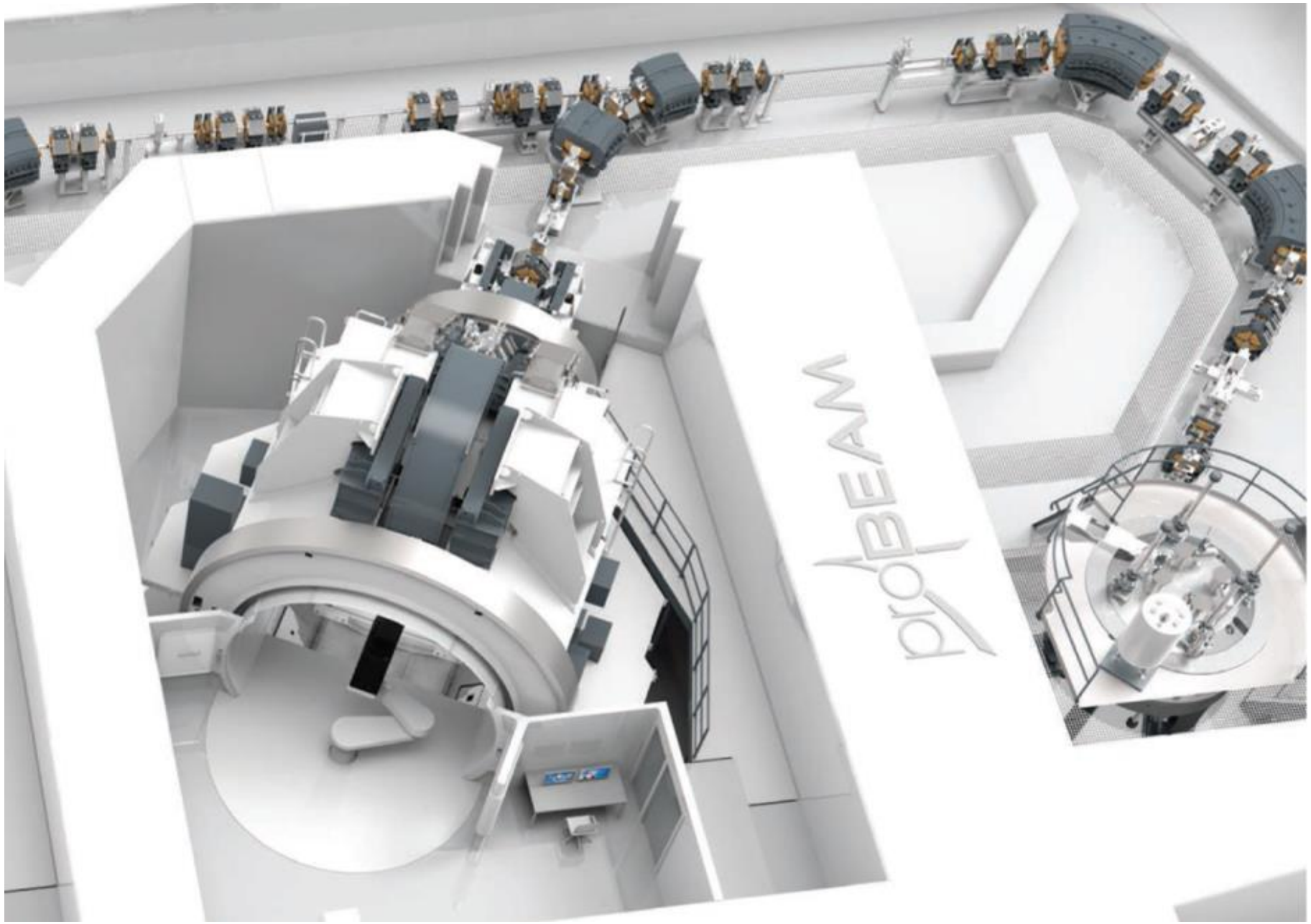
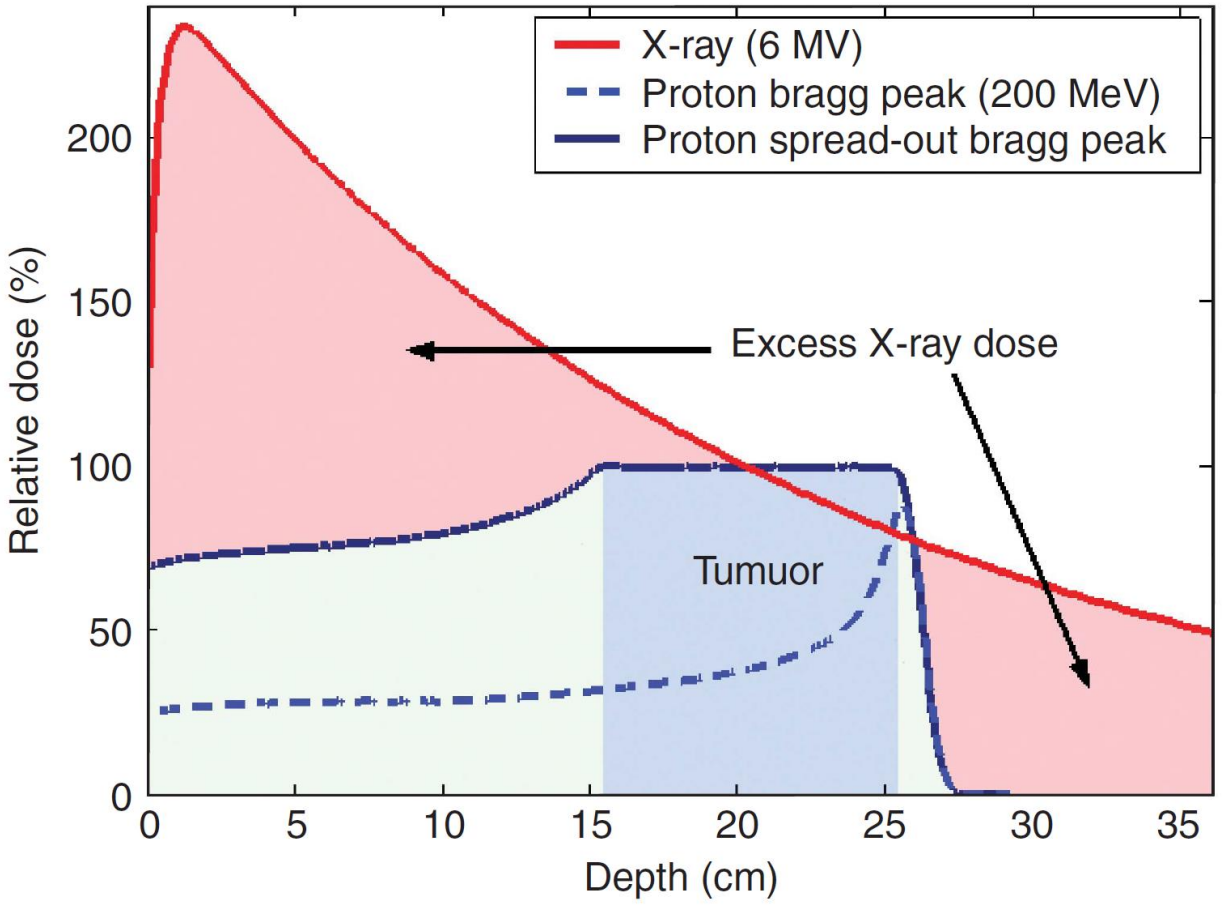
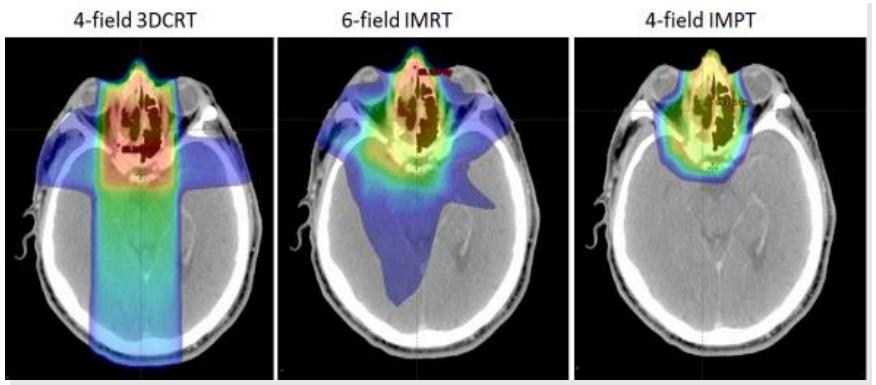
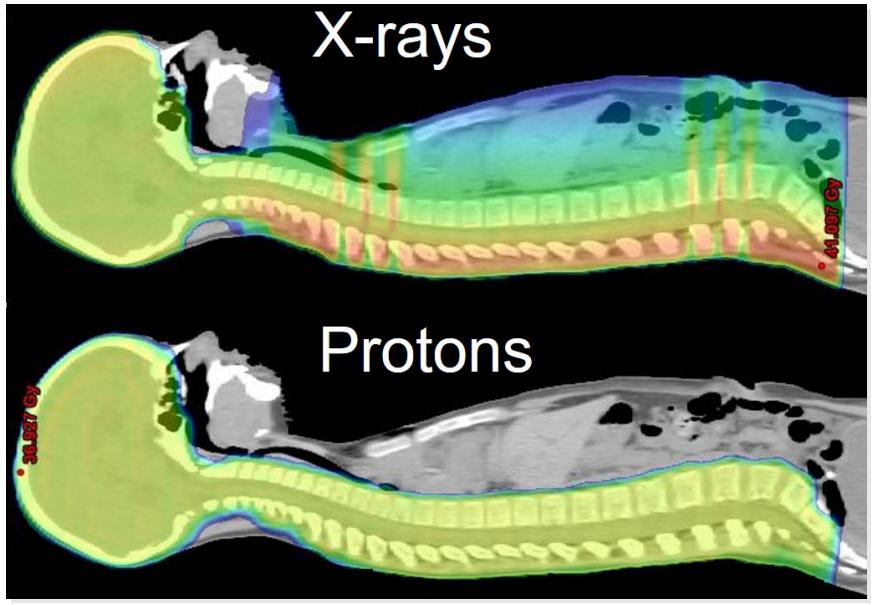

protBEAM

Advantageous dose distribution



Efstathiou JA et al, BJC, 2013





Aarhus University Hospital, 2013

Indications for proton therapy

- Reduce risk of serious complications, incl. risk of RT induced cancer
  - central nervous system
  - children and younger adults
  - all other situations where radiotherapy leads to significant morbidity
- Increase tumor control
  - Improved target coverage
  - Tumor dose escalation

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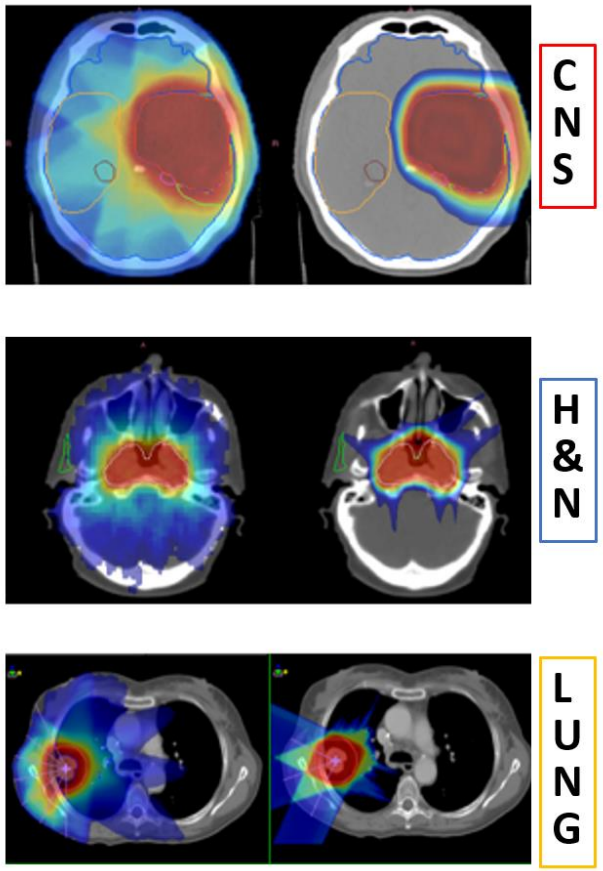
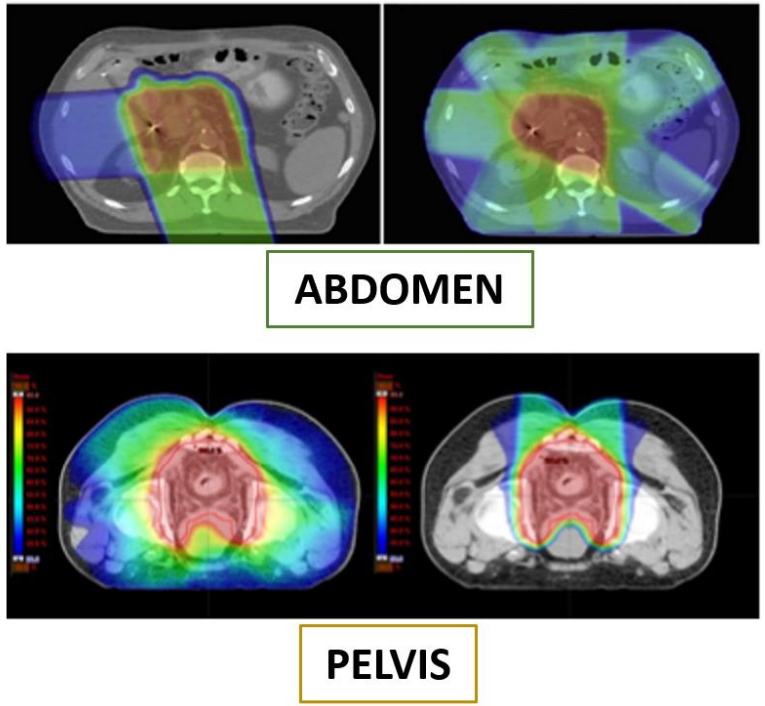
Advantageous dose distribution





- The dosimetric advantages of ion beam therapy have been well documented
- More than 300.000 patients have been treated with ion beam therapy since 1954
- Despite this long history, a superior clinical efficacy has not yet been clearly documented by high level **evidence**, i.e. randomized trials

Grau et. al. Mol Oncol. 2020

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Why are so few patients enrolled in randomized trials of novel technology?

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The CATCH-22 of expensive equipment

New technology is approved and marketed without any requirement of proof of clinical efficiency

Clinical evidence must be generated by the professional community. This requires access to the new technology

Clinical evidence is required to get funding of the heavy investments

Even if trials are performed, the technology is often outdated when the results are mature

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

Marco Durante[1,2], Roberto Orecchia[3,4] and Jay S. Loeffler[5,6]

NATURE REVIEWS | CLINICAL ONCOLOGY

VOLUME 14 | AUGUST 2017

2017

Only six ongoing randomized trials comparing protons and photons

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

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

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

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Durante et al. Nature Reviews, 2017

Esophageal cancer

Steven Lin et al, JCO 2020

Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer

Steven H. Lin, MD, PhD[1]; Brian P. Hobbs, PhD[2]; Vivek Verma, MD[3]; Rebecca S. Tidwell, PhD[4]; Grace L. Smith, MD, PhD, MPH[1,5]; Xiudong Lei, PhD[5]; Erin M. Corsini, MD[6]; Isabel Mok, RN[1]; Xiong Wei, MD[1]; Luyang Yao, MS[1]; Xin Wang, MD[7]; Ritsuko U. Komaki, MD[1]; Joe Y. Chang, MD, PhD[1]; Stephen G. Chun, MD[1]; Melenda D. Jeter, MD[1]; Stephen G. Swisher, MD[6]; Jaffer A. Ajani, MD[8]; Mariela Blum-Murphy, MD[8]; Ara A. Vaporciyan, MD[6]; Reza J. Mehran, MD[6]; Albert C. Koong, MD, PhD[1]; Saumil J. Gandhi, MD[1]; Wayne L. Hofstetter, MD[6]; Theodore S. Hong, MD[9]; Thomas F. Delaney, MD[9]; Zhongxing Liao, MD[1]; and Radhe Mohan, PhD[1]

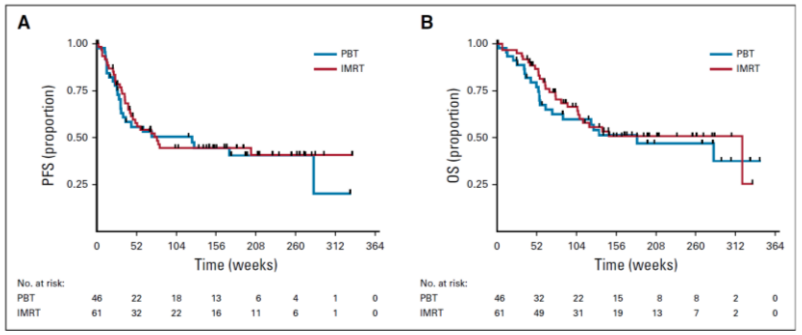
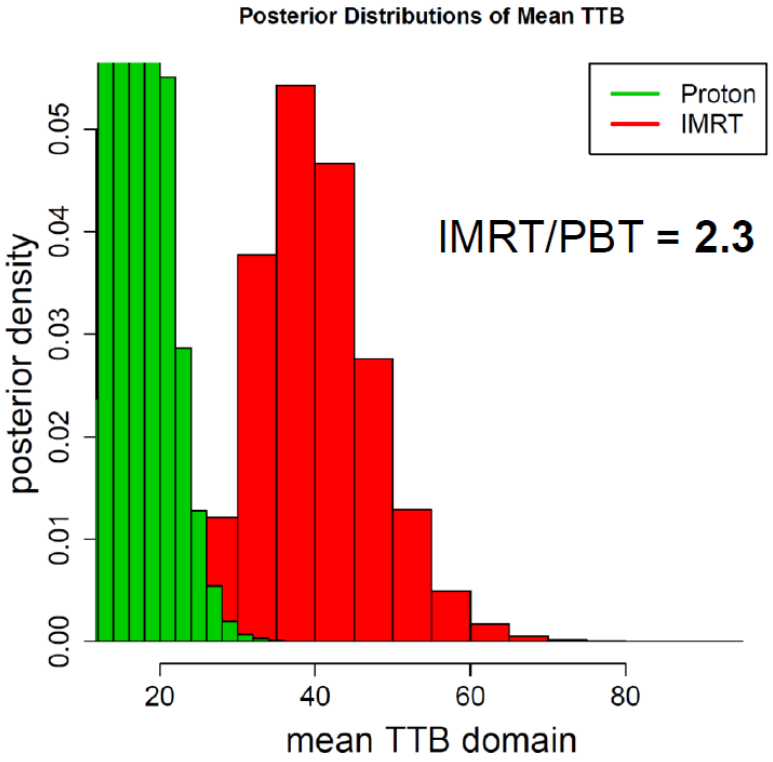


FIG 3. Kaplan-Meier (A) progression-free survival (PFS) and (B) overall survival (OS) curves between the proton beam therapy (PBT) and intensity-modulated radiation therapy (IMRT) arms.

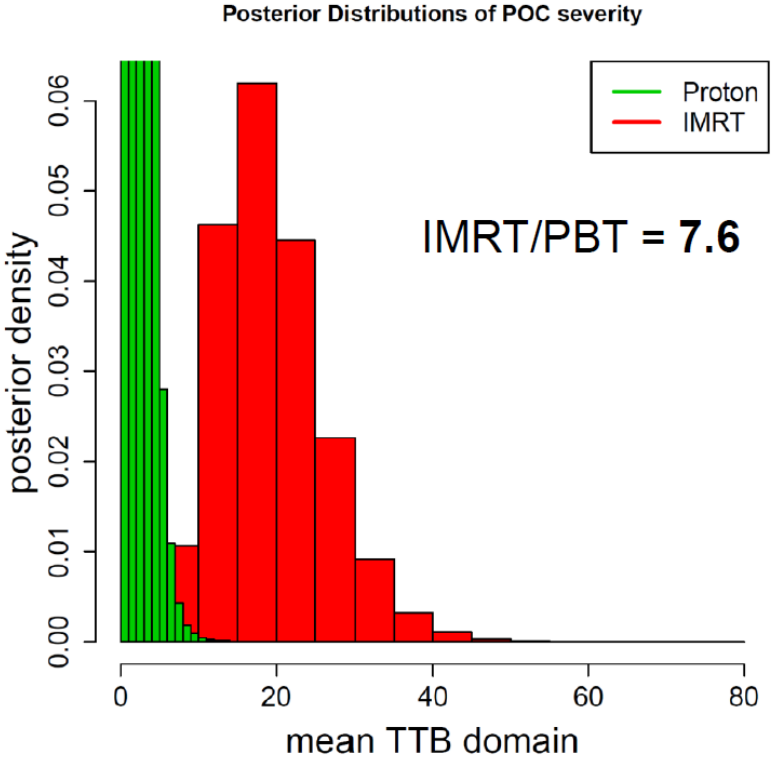
Total Toxicity Burden

IMRT: 39.9 (95% DI 26.2-54.9)
PBT: 17.4 (95% DI 10.5-25.0)



Postoperative Complications

IMRT: 19.1 (95% DI 7.3-32.3)
PBT: 2.5 (95% DI 0.3-5.2)



J Clin Oncol 38, 2020. https://doi.org/10.1200/JCO.19.02503

DCPT

Head and neck cancer

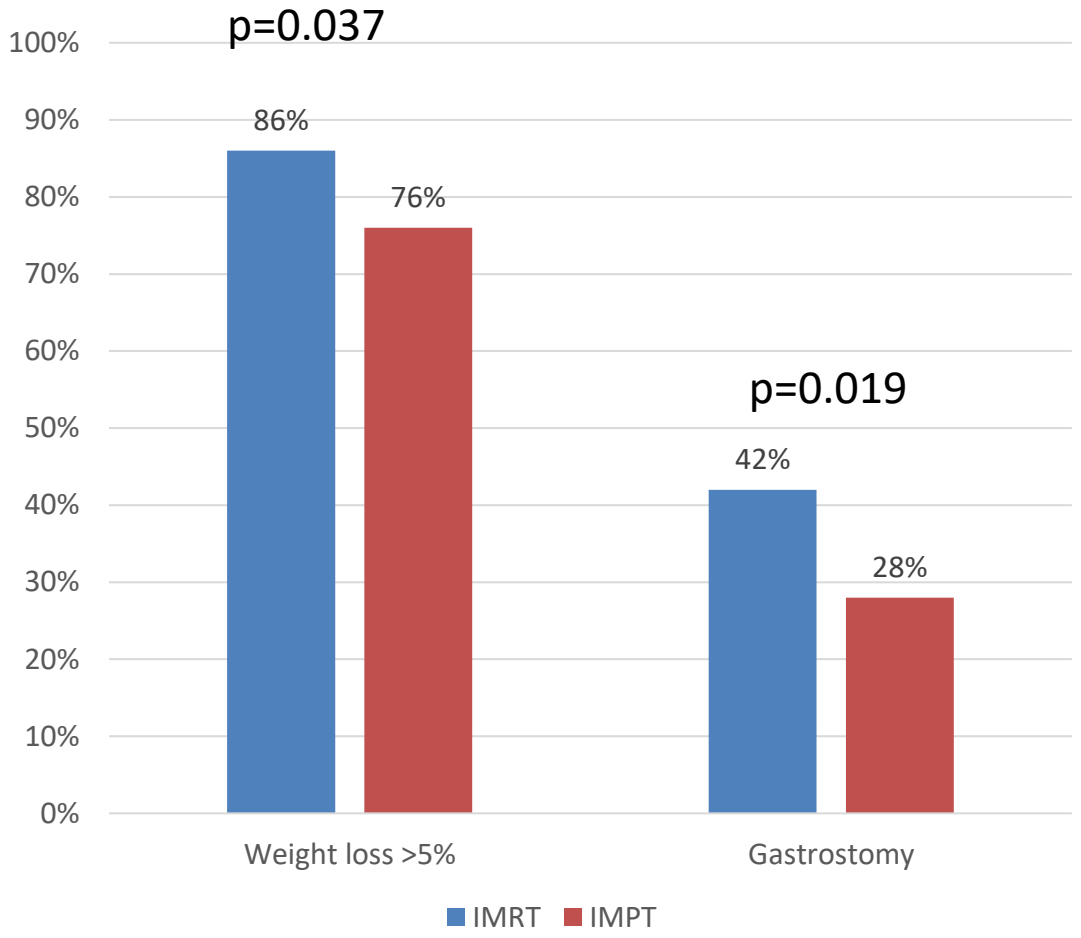
Steven Frank et al, ASCO 2024

6006 Oral Abstract Session

Phase III randomized trial of intensity-modulated proton therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for the treatment of head and neck oropharyngeal carcinoma (OPC).

Steven J. Frank, Paul Busse, David Ira Rosenthal, Mike Hernandez, David Michael Swanson, Adam S. Garden, Erich M. Sturgis, Renata Ferrarotto, Gary Brandon Gunn, Samir H Patel, NANCY Y. LEE, Alexander Lin, James W Snider, Mark William McDonald, Christina Henson, Gopal Krishna Bajaj, Noah Kalman, Upendra Parvathaneni, Sanford R. Katz, Robert Leonard Foote, MD Anderson Clinical Trial Consortium; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital, Boston, MA; Baylor College of Medicine, Houston, TX; Mayo Hosp, Phoenix, AZ; Memorial Sloan Kettering Cancer Center, New York, NY; University of Pennsylvania, Philadelphia, PA; The South Florida Proton Therapy Institute, Delray Beach, FL; Emory University Winship Cancer Institute, Atlanta, GA; Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK; Inova Fairfax Hospital, Fairfax, VA; Miami Cancer Institute, Miami, FL; University of Washington, Seattle, WA; Willis-Knighton Medical Center, Shreveport, LA; Mayo Clinic Department of Pediatric and Adolescent Medicine, Rochester, MN

Background: IMPT has unique biologic and physical properties compared with IMRT, limits radiation dose beyond the targeted tumor volumes, and is a novel de-intensification strategy for the management of head and neck tumors. This study was designed to compare the outcomes for patients with OPC after chemoradiation therapy (CRT) with IMRT vs IMPT. **Methods:** This is a multi-center, randomized, phase III non-inferiority OPC trial Stage III/IV (AJCC 7th) squamous cell carcinoma stratified patients by human papillomavirus status, smoking status, and receipt of induction chemotherapy (IC). The primary endpoint was the rate of progression-free survival (PFS) rate at 3 years, where progression was defined as disease recurrence or death. Under the null hypothesis, H0: $r \geq 1.535$ established the margin for non-inferiority of IMPT. Secondary endpoints include overall survival (OS), treatment-related malnutrition, and gastrostomy-tube dependence. Analyses were conducted on intent-to-treat (ITT; n=440), per-protocol (PP; n=296), and as-treated (AT; n=397) populations. **Results:** Patients (n=440) were randomized to undergo IMRT(n=219) or IMPT (n=221) at 21 institutions. The median age was 61 years and HPV/p16 was positive in 95%. IC was the initial treatment in 13% of patients. All patients were treated with CRT to 70 Gy in 33 fx with bilateral neck treatment, and post-CRT surgical lymph node dissection occurred in 8%. The median follow-up was 3.14 years. In the ITT analysis, the hazard ratio (HR) for disease progression or death at 3 y was 0.87 (95%CI 0.56,1.35); p=0.006 and the corresponding HR for death (OS) was 0.63 (95%CI 0.36-1.10) suggesting a protective affect with IMPT. In PP analysis, the PFS HR was 0.85 (95%CI 0.52,1.38); p=0.009 and HR for death (OS) was 0.60 (95%CI 0.32-1.12). In the AT analysis, PFS HR was 0.88 (95%CI 0.56,1.37); p=0.007 and the corresponding HR for death (OS) was 0.70 (95%CI 0.40-1.22). For each analysis above, the null hypothesis was rejected and IMPT was non-inferior to IMRT. PP gastrostomy-tube dependence decreased with IMPT vs. IMRT from 42% to 28% (p=0.019), and more IMPT patients sustained their nutrition with end of treatment weight loss < 5% from baseline: 24% vs 14% (p=0.037). **Conclusions:** IMPT is non-inferior to IMRT and has emerged as a standard of care CRT approach for OPC that reduces malnutrition and gastrostomy-tube dependence. Clinical trial information: NCT01893307. Research Sponsor: Hitachi.



INSURANCE BIAS – a problem in US trials:

- Patients randomized to IMRT are allowed protons by their insurance, and wants to be treated with IMPT
- Patients randomized to IMPT are denied insurance and will instead receive IMRT

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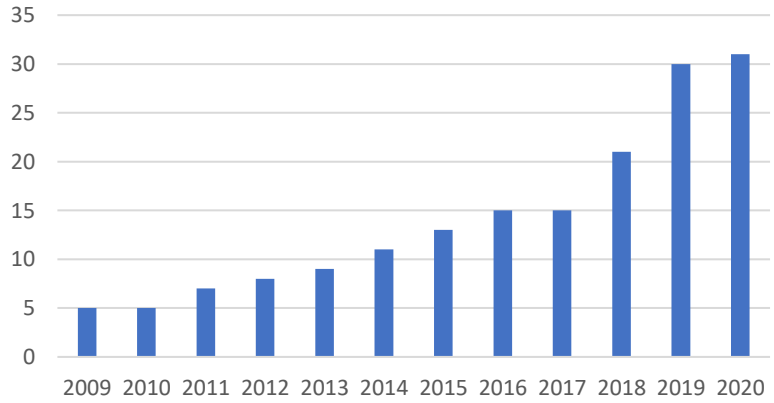
Proton therapy is becoming a reality in European countries

The number of European proton therapy clinical centres doubled from 2017 to 2020

- 2017: 15 operational facilities
- 2018: Six new facilities
- 2019: Eight new facilities
- 2020: 31 proton therapy facilities in clinical operation
- New facilities underway in Norway, Spain, Italy..



Source: PTCOG website. Accessed May 2023

European Particle Therapy Network (EPTN)

- Established in **2015 as a Task Force of ESTRO**
- **All European centres** involved in particle therapy
- **Mission** to promote **collaboration,** and to ensure that particle therapy becomes **integrated** in the overall radiation oncology community

- Clinical Evidence
- Quality Assurance
- Education
- Image Guidance
- Treatment Planning
- Radiobiology
- Health Economy

ESTRO

ClinicalTrials.gov 2024:
32 proton intervention trials recruiting in Europe

CNS	ProtoChoice-Hirn	II	no	346	Comparison of Proton and Photon Radiotherapy of Brain Tumors	Dresden, Heidelberg
CNS	PRO-CNS	II	no	500	Proton Radiotherapy for Primary Central Nervous System Tumours in Adults	Sweden
CNS	PRO-GLIO	II/III	yes	225	PROton Versus Photon Therapy in IDH-mutated Diffuse Grade II and III GLIOmas	Norway, Sweden
CNS	GRIPS	III	yes	326	Glioblastoma Radiotherapy Using IMRT or Proton Beams	Heidelberg
CNS	CSI ProLong	II	no	50	Proton Cranio-spinal Irradiation for Leptomeningeal Metastasis (CSI ProLong)	Denmark
CNS	GBM Dose escalated	I	no	36	Escalated Dose Proton Therapy Within the Multimodality Treatment of Glioblastoma Patients	Denmark
H&N	DAHANCA 37	II	no	20	Re-irradiation With Proton Radiotherapy	Denmark
H&N	ARTSCAN V	II	yes	100	Photon Therapy Versus Proton Therapy in Early Tonsil Cancer	Sweden
H&N	DAHANCA 35	III	yes	600	Proton Versus Photon Therapy for Head-neck Cancer	Denmark
H&N	TORPEdO	III	yes	183	A trial of proton beam radiotherapy for oropharyngeal cancer	UK
Thymus	PROTHYM	II	no	40	Study on Proton Radiotherapy of Thymic Malignancies	Sweden
Esophagus	PROTECT	III	yes	396	PROton Versus Photon Therapy for Esophageal Cancer - a Trimodality Strategy	DK, Europe
Breast	DBCG Proton (Skagen 2)	III	yes	1502	The DBCG Proton Trial: Photon Versus Proton Radiation Therapy for Early Breast Cancer	Denmark
Breast	PARABLE	III	yes	192	Proton beam therapy in patients with breast cancer: evaluating early and late effects	UK
Lung	HERAN2	II	yes	182	HERAN2 Heterogeneously Hypofractionated Radiotherapy for Locally Advanced NSCLC	Denmark
Lung	PRONTOX	II	yes	98	Proton Therapy to Reduce Acute Normal Tissue Toxicity in Locally Advanced Non-small-cell Lung Cancer	Dresden, Heidelberg
Liver	HCC Proton	II	no	50	A National Phase II Study of Proton Therapy in Hepatocellular Carcinoma	Denmark
Pancreas	LAPC	II	no	30	Radiotherapy for Locally Advanced Pancreatic Carcinomas	MedAustron
Pancreas	PARC	II	no	10	Preoperative, Proton- Radiotherapy Combined With Chemotherapy for Borderline Resectable Pancreatic Cancer	MedAustron
Rectal	ReRad II	II	no	65	Pencil Beam Proton Therapy for Pelvic Recurrences in Rectal Cancer Patients Previously Treated With Radiotherapy	Denmark
Rectal	PRORECT	III	yes	254	Preoperative Short-Course Radiation Therapy With PROtons Compared to Photons In High-Risk RECTal Cancer	Sweden
Cervix	PROTECT	II	no	30	On-line Adaptive Proton Therapy for Cervical Cancer to Reduce the Impact on Morbidity and the Immune System	HollandPTC
Anal	DACG5, ReRad III	II	no	55	Pencil Beam Proton Therapy for Recurrences in Anal Cancer Patients Previously Treated With Radiotherapy	Denmark
Anal	SWANCA	II	yes	100	Proton Versus Photon Therapy in Anal Squamous Cell Carcinoma Swedish Anal Carcinoma Study	Sweden
Prostate	ProtoChoice-P	II	no	146	Preference-based Comparative Study on Definitive Radiotherapy of Prostate Cancer With Protons	Heidelberg
Prostate	N/A	II	no	297	Spot-Scanning Based Hypofractionated Proton Therapy for Low and Intermediate Risk Prostate Cancer	MedAustron
Prostate	PRO-PROTON 1	III	yes	400	Protons vs. Photons for High-risk Prostate Cancer	Denmark
Prostate	PAROS	III	yes	897	Prostate Cancer Patients Treated With Alternative Radiation Oncology Strategies	Heidelberg
Sarcoma	EXTREM-ION	II	yes	42	Neoadjuvant Irradiation of Extremity Soft Tissue Sarcoma With Ions	Heidelberg
Sarcoma	ISAC	II	yes	100	Ion Irradiation of Sacrococcygeal Chordoma (Proton vs Carbon)	Heidelberg
Sarcoma	RETRO ION	II	yes	64	Neoadjuvant Irradiation of Retroperitoneal Soft Tissue Sarcoma With (Proton vs Carbon)	Heidelberg
Sarcoma	ETOILE	III	yes	250	Randomized Carbon Ions vs Standard Radiotherapy (incl. protons) for Radioresistant Tumors	France, C+ centres

Per 2023

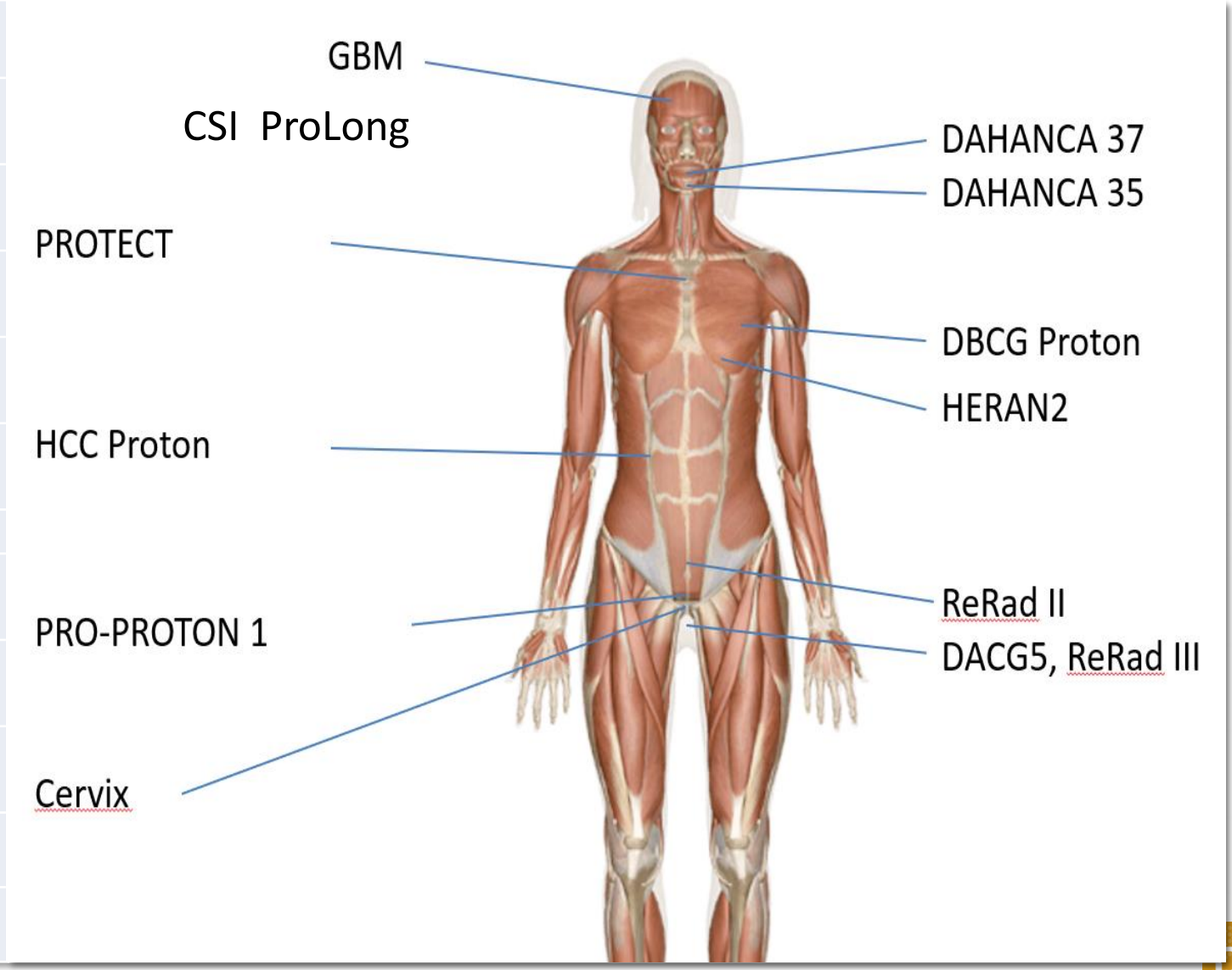
Total n=32

Phase II=20
Phase III=11
Randomized=18

DE 8
DK 11
SE 6
AU 3
NL 1
UK 2
FR 1

Clinical proton intervention studies DCPT 2024

Tumor Site	Protocol	Phase	Rand	n
BREAST	DBCG Proton (Skagen 2)	III	yes	1502
HEAD & NECK	DAHANCA 37	II	no	20
HEAD & NECK	DAHANCA 35	III	yes	600
PROSTATE	PRO-PROTON 1	III	yes	400
ANAL	DACG5, ReRad III	II	no	55
LIVER	HCC Proton	II	no	50
RECTAL	ReRad II	II	no	65
ESOPHAGUS	PROTECT	III	yes	396
LUNG	HERAN2	II	yes	182
CNS	CSI ProLong	II	no	99
CNS	GBM Dose escalat	I	no	36

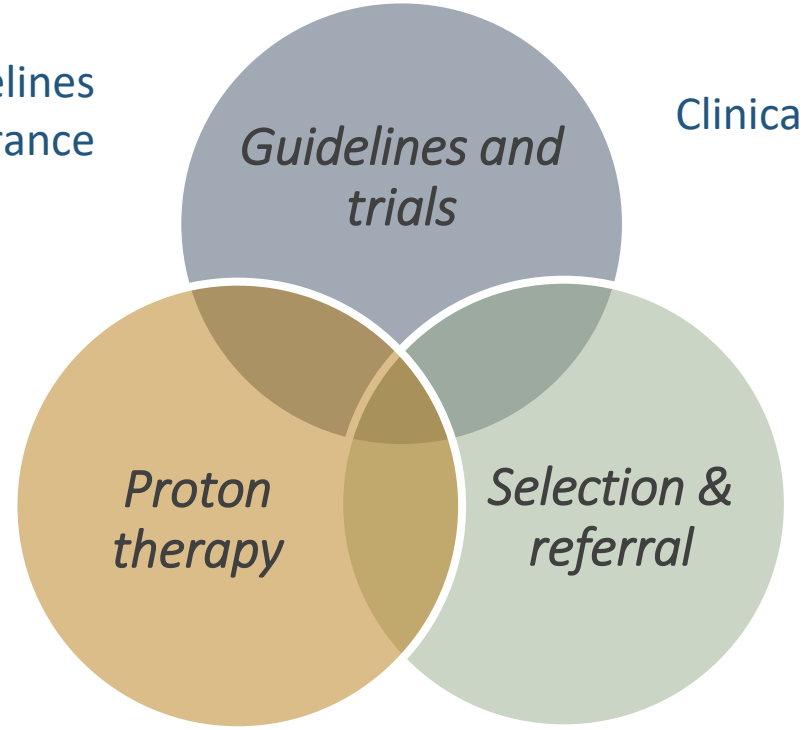


Danish national model for collaboration

Danish Multidisciplinary Cancer Groups (DMCG's)

National guidelines
Quality assurance

Clinical trials



Proton treatment
Trial support

DCPT

Patient accrual
Referral
Follow-up

Oncology departments

Trial inclusion - the Danish Centre for Particle Therapy

Revision date 31.12.2023

2019-2023: 693 patients in clinical trials (70%)

Diagnosis	Protocol title	Incl. start date	Expected no. (DK)	Total no. included in pilot study	Total no. included (DK)	Total no. treated at DCPT	No. included during the last year
Anal cancer	ReRad III	01.07.2021	55		11	11	7
Breast cancer	Skagen II	04.06.2020	1502	40	237	114	89
Brain tumours	DNOG2	04.01.2019	300		268	193	58
	CSI ProLong	05.09.2023	99		0	0	0
Head and neck cancer	DAHANCA 30	26.08.2020	–		–	67	20
	DAHANCA 35	21.09.2020	327/216	63	158	101	54
	DAHANCA 37	01.01.2020	20		11	11	0
Hepatocellular carcinoma	HCC PROTON	15.04.2022	50		28	28	22
Lung cancer	HERAN2	15.10.2022	200	5	–	–	–
Oesophageal cancer	PROTECT	01.08.2022	International trial		19	9	12
Prostate cancer	PRO-PROTON 1	01.02.2022	400	24	9	7	9
Rectal cancer	ReRad II	01.10.2020	63+66		21	21	9
Pediatric cancers							
Rabdomyosarcoma	FaR-Rms	15.11.2020	International trial		–	8	5
Ependymoma	EP II	01.12.2020	International trial		–	4	1
Proton treatment	HARMONIC	27.12.2020	90		46	46	18
Medulloblastoma	HR-MB	30.03.2022	International trial		–	3	1
Neuroblastoma	HR-NBL2	16.06.2022	International trial		–	4	4
Atypical teratoid/rhabdoid tumours	AT-RT-01	16.01.2023	International trial		–	1	1
Different diagnosis	TEDDI	15.02.2022	International trial		–	0	0

DAHANCA 35

Candidates
- SCC of the pharynx or larynx (excl. st. 1/2 glottic larynx)
- Indication for radiotherapy with curative intent

Doseplan comparison
Proton/photon
ΔNTCP >5% for either dysphagia or xerostomia

- DAHANCA dysphagia score >= grade 2
- Severe xerostomia (EORTC HN 35)

No → **ΔNCPT < 5%**
- Treatment and follow-up according to routine guidelines

Yes

Selected for dysphagia
Randomisation
Protons vs photons 2:1

Selected for xerostomia Randomisation
Protons vs photons 2:1

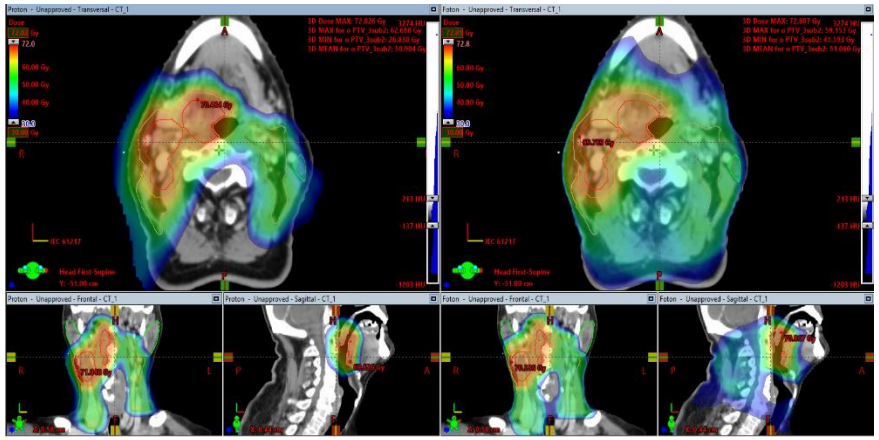
Primary endpoints

Dysphagia (n=327)
Assessed at 6 months

Xerostomia (n=216)
Assessed at 6 months

Secondary endpoints analysed for both groups combined

PI: Jeppe Friborg



Pilot phase (2019/2020))
63 patients

Randomised study (2021-)
175 patients randomized per June, 2024

PROTECT trial

radiation against esophageal cancer

PROton versus photon radiation Therapy for Esophageal Cancer in a Trimodality strategy (PROTECT)

A multicentre international randomized phase III study of neoadjuvant proton based chemoradiotherapy in locally advanced esophageal cancer

imi innovative medicines initiative

efpia

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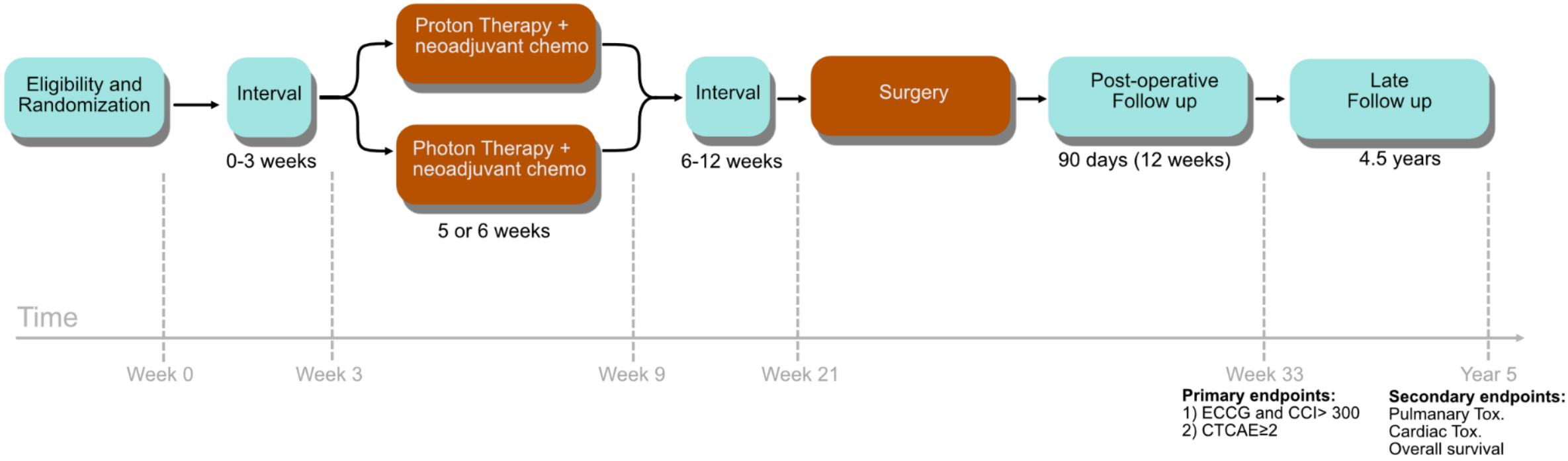
DCPT

Multicentre international randomized phase III study



PROTECT trial

Public-private partnership

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NHS The Christie NHS Foundation Trust
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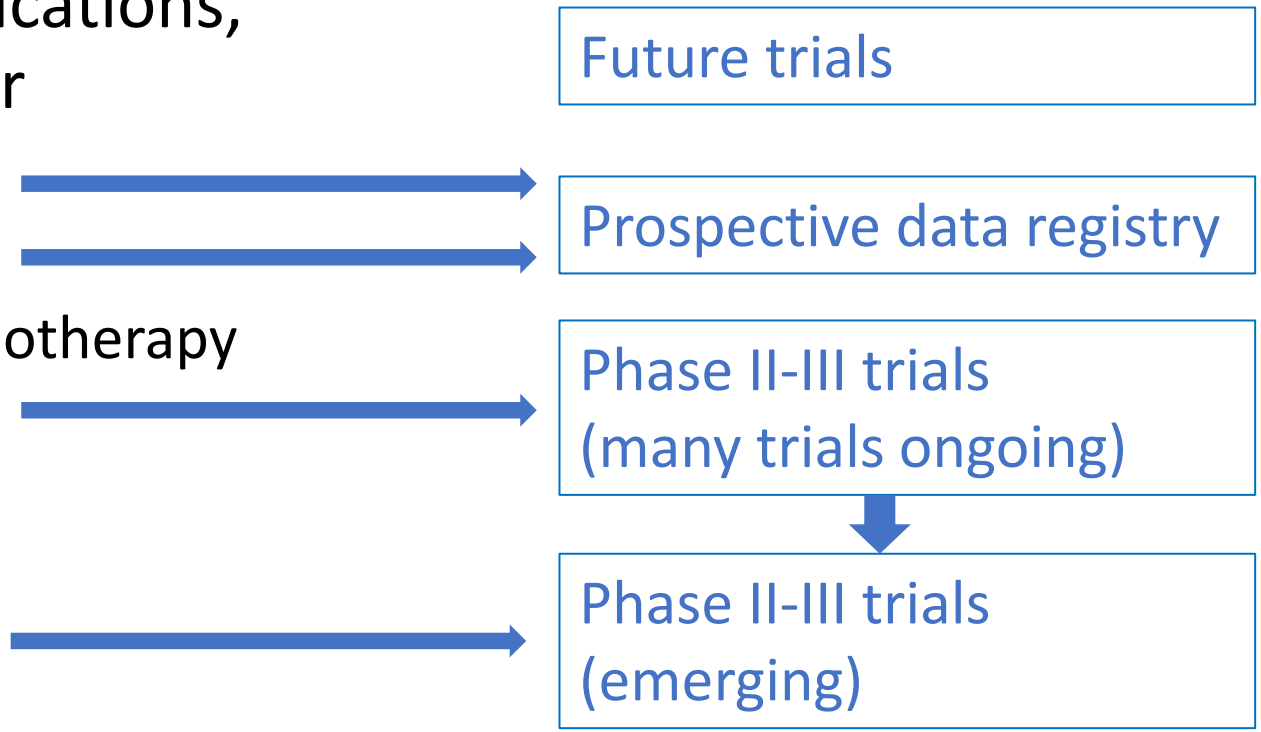
institut Curie
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
varian A Siemens Healthineers Company
iba
imi innovative medicines initiative
efpia

PROTECT trial

Indications for proton therapy

- Reduce risk of serious complications, incl. risk of RT induced cancer
  - central nervous system
  - children and younger adults
  - all other situations where radiotherapy leads to significant morbidity
- Increase tumor control
  - Improved target coverage
  - Tumor dose escalation



Conclusions

- With a few exceptions, the role of proton therapy in radiation oncology and cancer management remains unsettled
- It is encouraging that we now have more than 30 European interventional trials underway, predominantly testing morbidity reduction
- Future trials will focus on improved loco-regional control and survival
- The results of these pivotal trials will be defining for the uptake of proton therapy in the future

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