

Capital Markets Day

2019 ASTRO Annual Meeting

16 September 2019





IBA strategy and business update

Olivier Legrain, Chief Executive Officer, IBA Jeroen Cammeraat, Chief Market Officer, IBA

Proton Therapy status and future directions – a practitioner's perspective

Jing Zeng, MD, Associate Professor of Radiation Oncology, University of Washington, Seattle / Associate Medical Director, SCCA Proton Therapy Center

The latest milestones in Proton Therapy innovation, including FLASH

Nicolas Denef, Director of Product Management, IBA

Question and answer

Disclaimer



This presentation may contain forward-looking statements concerning industry outlook, including growth drivers; the company's future orders, revenues, backlog, or earnings growth; future financial results; market acceptance of or transition to new products or technology and any statements using the terms "could," "believe," "outlook," or similar statements are forward-looking statements that involve risks and uncertainties that could cause the company's actual results to differ materially from those anticipated. The company assumes no obligation to update or revise the forward-looking statements in this release because of new information, future events, or otherwise.

H1 2019 overview



Revenue

PT and Other Accelerators EUR 102.8M (+13.8%) Dosimetry EUR 25.3M (+3.9%)

Sales

7 PT rooms 15 Other Accelerators

Order intake: EUR 133.4M

Backlog

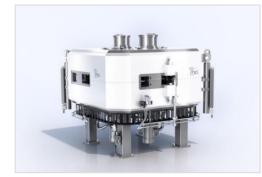
Equipment: EUR 342M Service: EUR 747M

Operations

53 PT centers sold

29 centers in operation24 centers in development









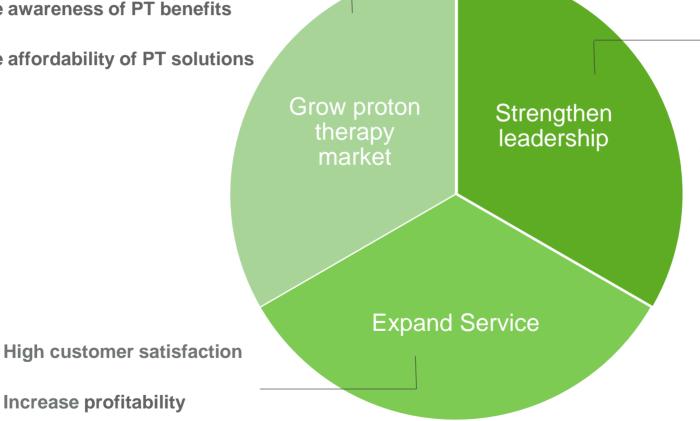
Long term strategy for growth

Facilitate evidence generation •

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- Increase awareness of PT benefits
- Increase affordability of PT solutions •



- Superior clinical technology •
- Fastest installation in the market •
- **Reliability of IBA equipment** •
- Upgradability of systems
- **Strategic partnerships**

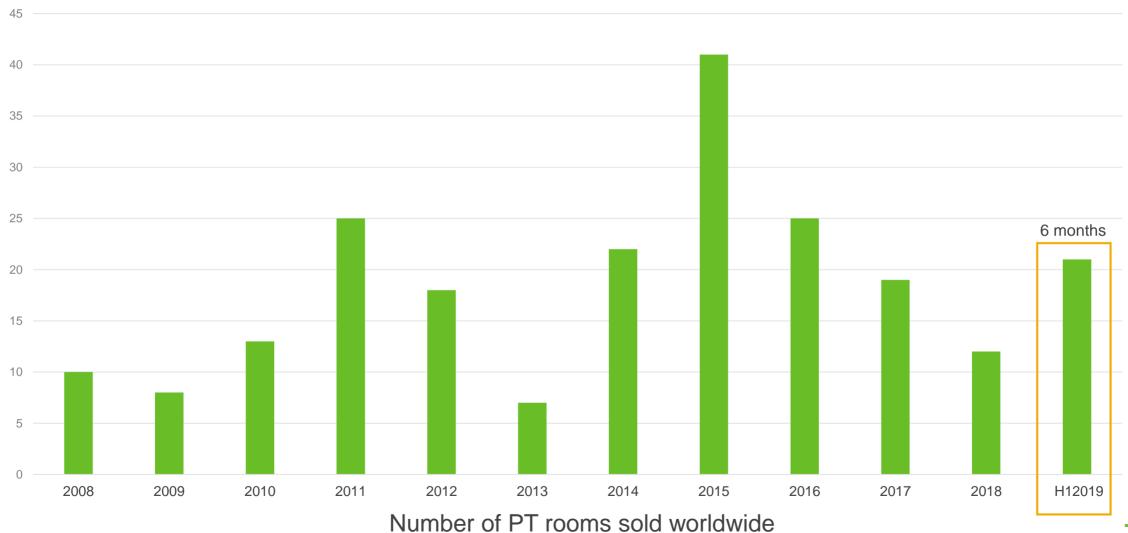
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Extension of Service offering •

(ba

Proton Therapy Market Evolution

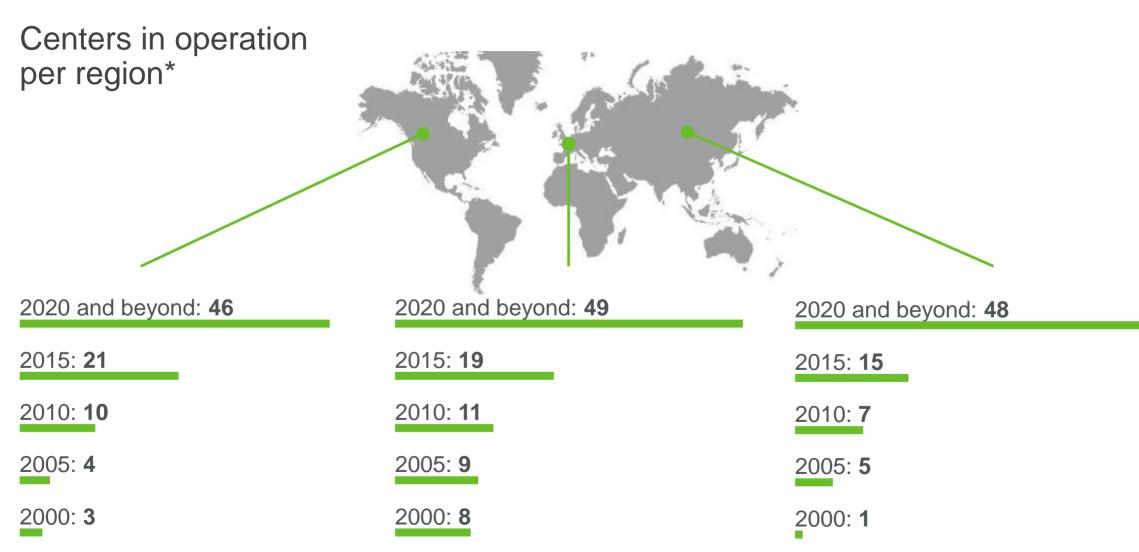
Evolution of the proton therapy market



lhc

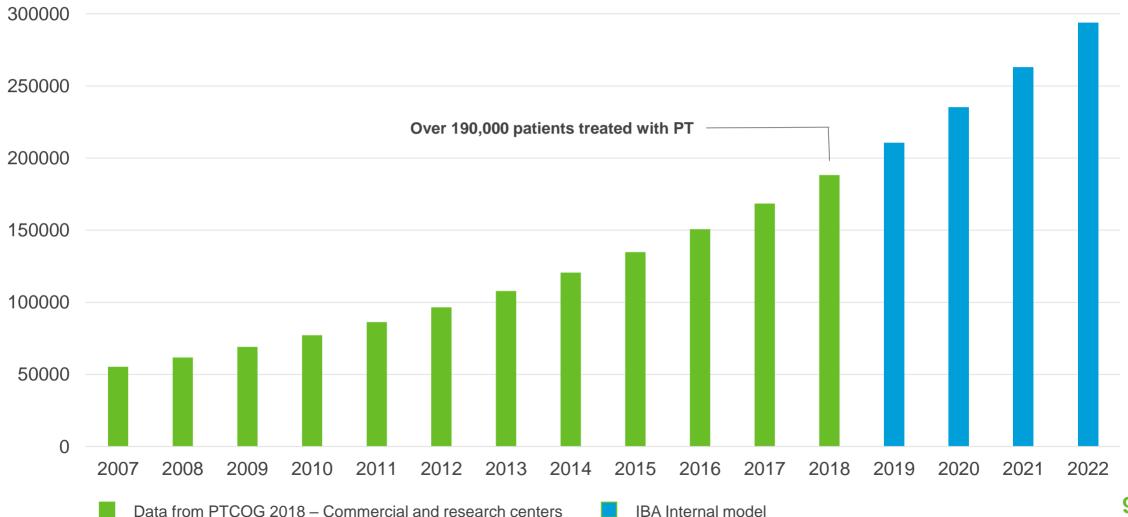
Proton therapy is growing





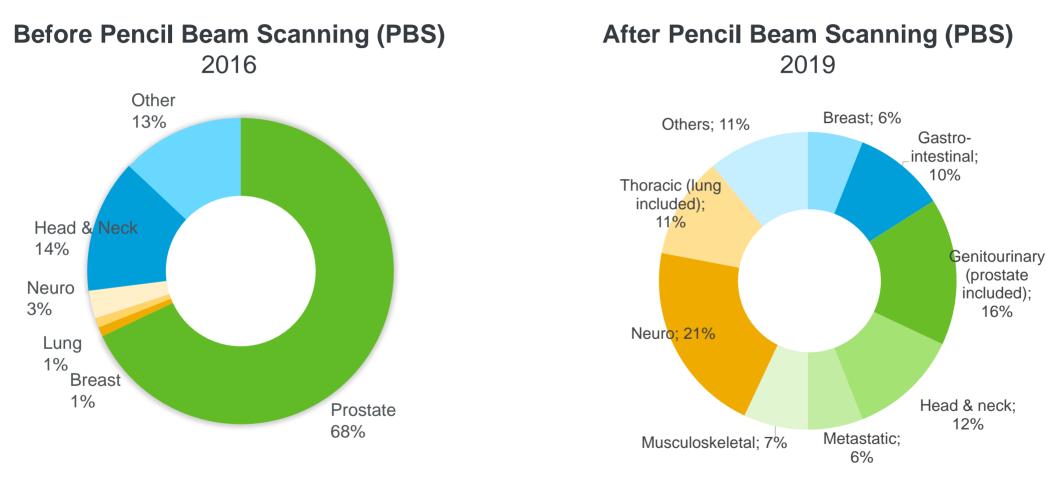
* PTCOG 2019 Data including centers with eye treatments only

Number of patients treated with PT is growing fast









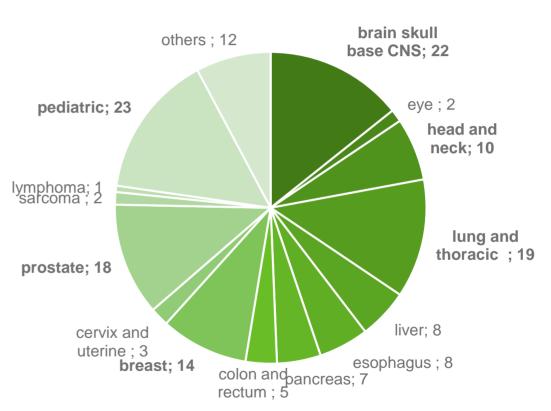
Typical cancer indications treated (% patients)

(data from a leading center in the US)

High activity in peer reviewed publications and trials



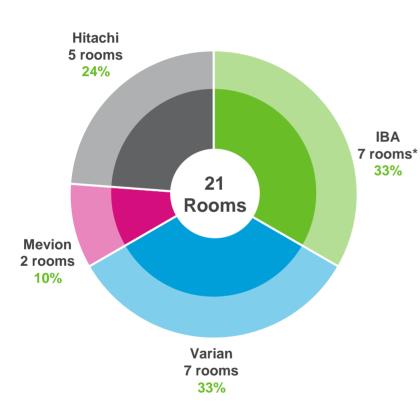
150+ clinical trials ongoing on PT



Number of publications up to end of 2018 PubMed database lha

IBA Leading Market Share

PT centers sold in 2019

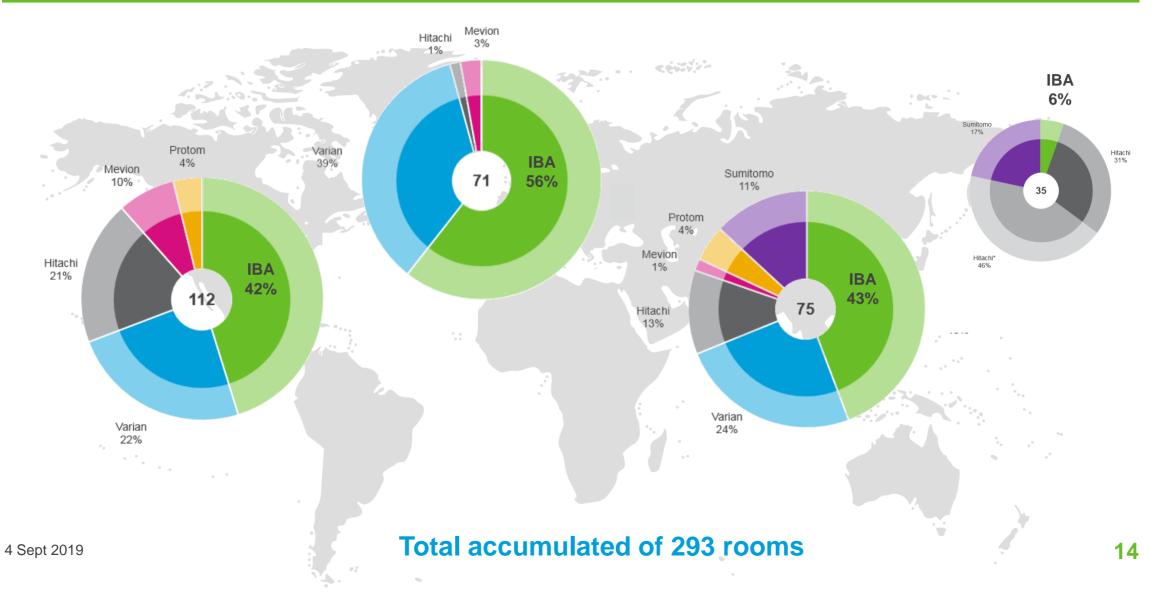


Center	No of clinical PT rooms	Region	Vendor
University of Kansas Hospital	1	North America	IBA
IEO Milano	1	Europe	IBA
Shenzhen Tumor Hospital	5	Asia	IBA
MD Anderson Cancer Center	4	North America	Hitachi
Himed Hospital Management	1	Asia	Hitachi
Haukeland University (Bergen)	1	Europe	Varian
Oslo Universitetssykehus Hf	3	Europe	Varian
Shandong Cancer Hospital	3	Asia	Varian
Allcure Kangtai	1	Asia	Mevion
Mercy Hospital	1	North America	Mevion
Total	21		

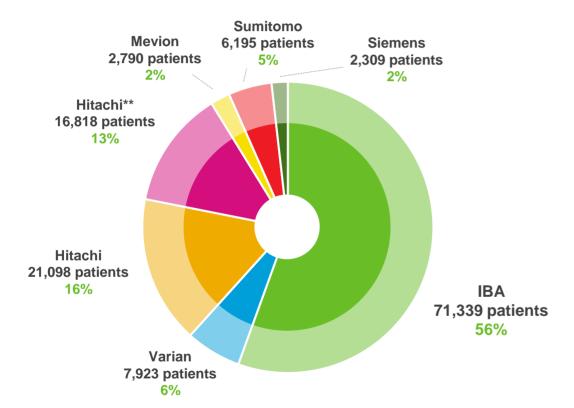
- 21 rooms sold in 2019 (versus 5 in first half 2018)
 - 5 in Europe
 - 6 in North America
 - 10 in Asia

IBA – a global leader in proton therapy

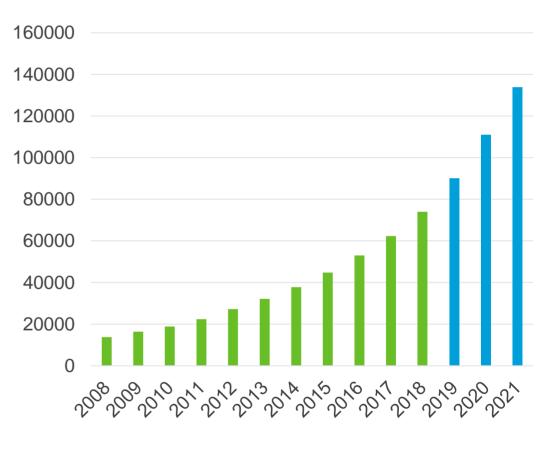








Cumulative patients treated by centers with IBA solutions



Data from PTCOG 2018 - Commercial centers only

Data from PTCOG 2018

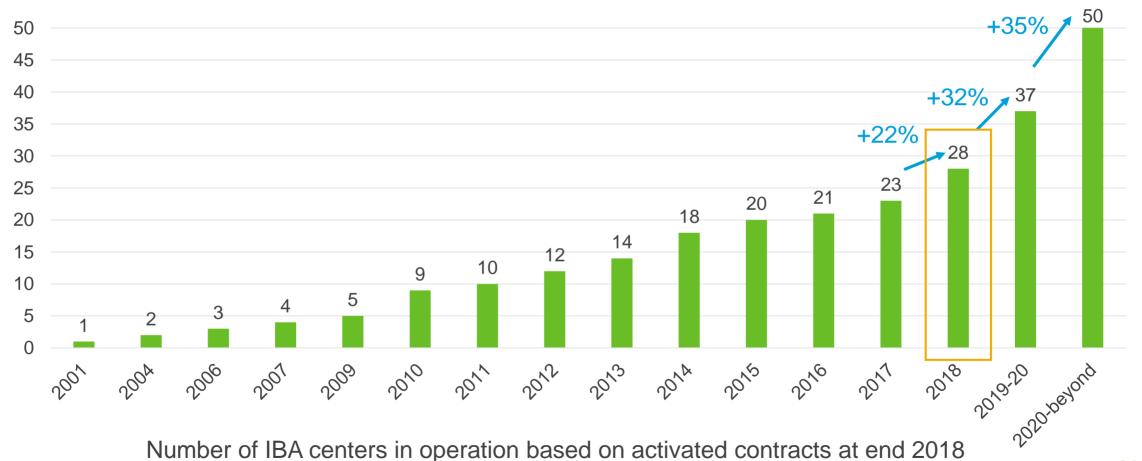
IBA Growing Service



Number of IBA PT centers in operation is growing fast

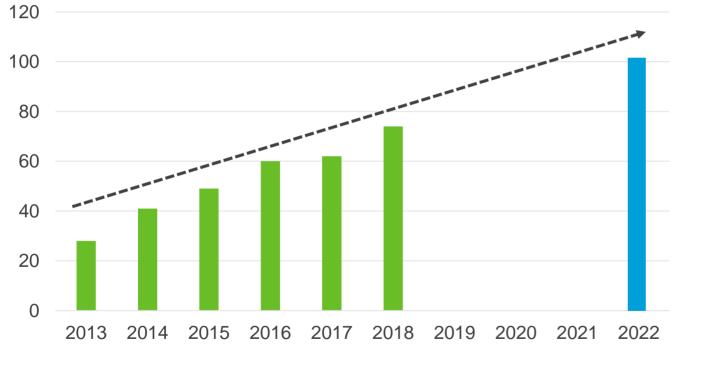


From 29 centers in operation today to 50+ beyond 2020





EUR 747M backlog in service



Service revenues for PT alone expected to exceed EUR 100M

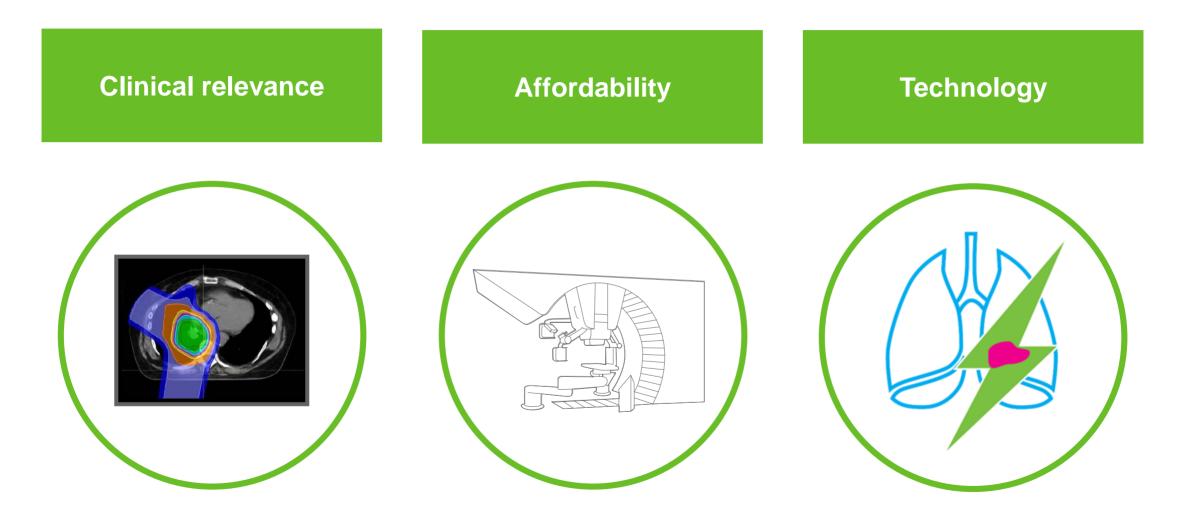
By 2022

PT Service Revenues (M euros)

Accelerating proton therapy adoption

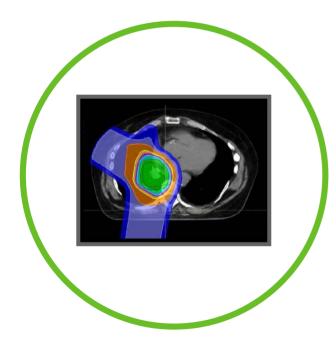
Three key axes of development







Clinical relevance



IBA initiatives

IBA Victoria Advisory Committee

 Consortium of international radiation therapy experts defining the future of proton therapy

IBA PT Users meeting

 Users define opportunities for innovation and new indications as well as clinical studies and treatment protocols

Support of Model-based approach

Select suitable patients for proton therapy (comparing photons versus protons)

Support of Proton Collaborative Group (PCG)

 Developing new research protocols and sharing those results across multiple treatment centers

Support Patient Advocacy Groups (e.g. Alliance)

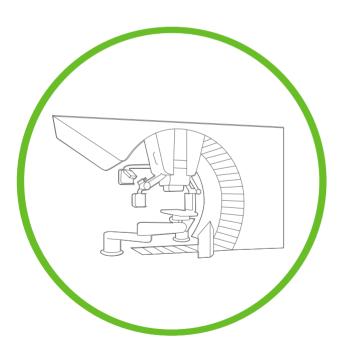
Focused on PT insurance reform through patient advocacy

Raise awareness for Proton Therapy benefits

- Facilitate multidisciplinary focus groups
- Expand symposiums on PT
- Publicize white papers



Affordability



IBA initiatives

- Reduction of treatment cost
 - Research on hypofractionated proton therapy (e.g. FLASH)
 - Reduction of equipment cost
 - Reduction of PT clinical workflow
 - Reduction of installation time
 - Focus on availability of IBA systems (uptime of 98%)



Technology



IBA initiatives

Accelerating research in proton therapy

- Continued clinical innovation with our partners
- FLASH, ARC, Motion Management

Strong partnerships with RT leaders

Philips, RaySearch, Elekta, Varian

• All systems upgradable to the latest technology

Maximize treatment efficiency



Q&A





Proton Therapy: Current Status & Future Directions – A Practitioner's Perspective

Jing Zeng, MD

Associate Professor, Department of Radiation Oncology University of Washington School of Medicine Associate Medical Director, SCCA Proton Therapy Center

IBA Meeting, September 16th, 2019, Chicago, IL

General Radiation Principles

- There is no benefit to radiation to normal tissues
- <u>ALARA As Low As Reasonably Achievable</u>: accepted as standard clinical practice without clinical trial evidence
 - Worldwide acceptance of proton therapy for children
 - Low-dose CT scanners: no randomized trials required for deployment

General Radiation Principles

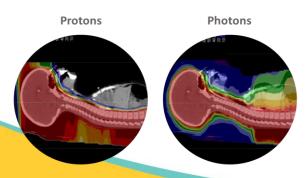
- However, healthcare resources are finite
 - We must be good stewards of expensive and labor-intensive technology
 - Must prove VALUE

Evolution of Proton Therapy Research

Single Modality Patient Series Retrospective Comparisons of Protons vs. Photons

Randomized Clinical Trials of Protons vs. Photons

Dosimetric Comparisons



Proving Value:

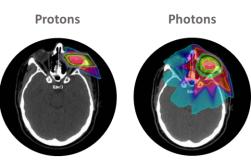
- Cost effectiveness (cost of toxicity and quality of life)
- Modeling to predict benefit

Biology of Protons:

- Interaction with systemic therapy
- Differential effects on tumor

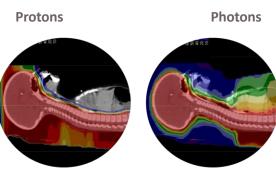
Images represent a reduction in radiation to the entire chest and abdomen cavities, when using protons

Ocular Tumors



Decrease in radiation exposure to underlying brain tissue, when using protons

Medulloblastoma: Craniospinal Irradiation

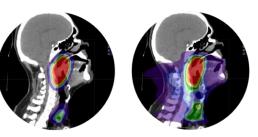


Images represent a reduction in radiation to the entire chest and abdomen cavities, when using Confidential | ProprietaryProtons

Head & Neck Cancers

Protons

Photons

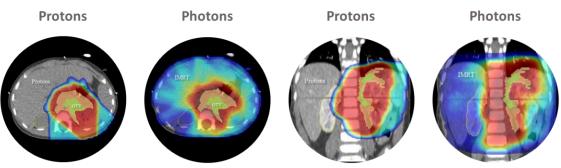


Images represent a reduction in radiation to the head and brain, when using protons

Seattle Cancer Care Alliance Fred Hutch · Seattle Children's · UW Medicine



Pediatric Neuroblastoma



Images represent a reduction in radiation to the abdomen, when using protons

Retrospective Series on Proton Therapy

CLINICAL INVESTIGATION

Prostate

PROTON THERAPY FOR PROSTATE CANCER: THE INITIAL LOMA LINDA UNIVERSITY EXPERIENCE

JERRY D. SLATER, M.D., CARL J. ROSSI, JR., M.D., LES T. YONEMOTO, M.D., DAVID A. BUSH, M.D., B. RODNEY JABOLA, M.D., RICHARD P. LEVY, M.D., PH.D., ROGER I. GROVE, M.P.H., WILLIAM PRESTON, ED.D., AND JAMES M. SLATER, M.D., F.A.C.R.

Department of Radiation Medicine, Loma Linda University Medical Center, Loma Linda, CA

Clinical Investigation

Early Cognitive Outcomes Following Proton Radiation in Pediatric Patients With Brain and Central Nervous System Tumors

Margaret B. Pulsifer, PhD,* Roshan V. Sethi, MD,[†] Karen A. Kuhlthau, PhD,[‡] Shannon M. MacDonald, MD,[†] Nancy J. Tarbell, MD,[†] and Torunn I. Yock, MD[†]



International Journal of Radiation Oncology

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Prospective Trials on Proton Therapy

JAMA Oncology | Original Investigation

Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer Final Results of a Phase 2 Study

Joe Y. Chang, MD, PhD; Vivek Verma, MD; Ming Li, MD; Wencheng Zhang, MD; Ritsuko Komaki, MD; Charles Lu, MD; Pamela K. Allen, PhD; Zhongxing Liao, MD; James Welsh, MD; Steven H. Lin, MD, PhD; Daniel Gomez, MD; Melenda Jeter, MD; Michael O'Reilly, MD; Ronald X. Zhu, PhD; Xiaodong Zhang, PhD; Heng Li, PhD; Radhe Mohan, PhD; John V. Heymach, MD, PhD; Ara A. Vaporciyan, MD; Stephen Hahn, MD; James D. Cox, MD International Journal of Radiation Oncology biology • physics

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Clinical Investigation: Genitourinary Cancer

Five-Year Outcomes from 3 Prospective Trials of Image-Guided Proton Therapy for Prostate Cancer

Nancy P. Mendenhall, MD,* Bradford S. Hoppe, MD,* Romaine C. Nichols, MD,* William M. Mendenhall, MD,* Christopher G. Morris, MS,* Zuofeng Li, DSc,* Zhong Su, PhD,* Christopher R. Williams, MD,[†] Joseph Costa, DO,[†] and Randal H. Henderson, MD, MBA*

*University of Florida Proton Therapy Institute, Jacksonville, Florida; and [†]Division of Urology, College of Medicine, University of Florida, Jacksonville, Florida

Received Sep 7, 2013, and in revised form Oct 30, 2013. Accepted for publication Nov 4, 2013.

Retrospective Comparisons

Clinical Investigation

Clinical Outcomes Among Children With Standard-Risk Medulloblastoma Treated With Proton and Photon Radiation Therapy: A Comparison of Disease Control and Overall Survival

Bree R. Eaton, MD,* Natia Esiashvili, MD,* Sungjin Kim, MS,[†] Elizabeth A. Weyman, B.A.,[‡] Lauren T. Thornton, B.S.,[‡] Claire Mazewski, MD,[§] Tobey MacDonald, MD,[§] David Ebb, MD,^{||} Shannon M. MacDonald, MD,[‡] Nancy J. Tarbell, MD,[‡] and Torunn I. Yock, MD[‡]



International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis



Prospective Randomized Clinical Trials

- Prostate: PARTIQoL, COMPPARE
- Breast: RAD-COMP
- Brain: NRG-BN001, NRG-BN005
- Lung: RTOG 1308
- Esophageal: NRG-GI006
- Liver: NRG-GI003

Prospective Randomized Clinical Trials

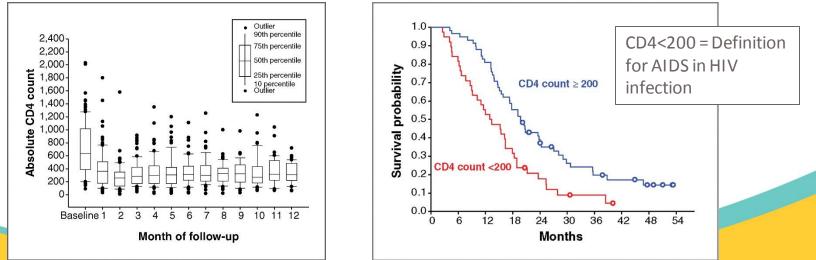
- Prostate: PARTIQoL, COMPPARE
- Breast: RAD-COMP
- Brain: NRG-BN001, NRG-BN005
- Lung: RTOG 1308
- Esophageal: NRG-GI006
- Liver: NRG-GI003

Biology of Protons

- Decreased radiation to the body = less immune suppression?
 - Lymphopenia
 - Less radiation to draining lymph nodes and other immune cells
- Different biological action
 - More immunogenic?
 - Better killing of resistant cell types?

Radiation Is Immunosuppressive

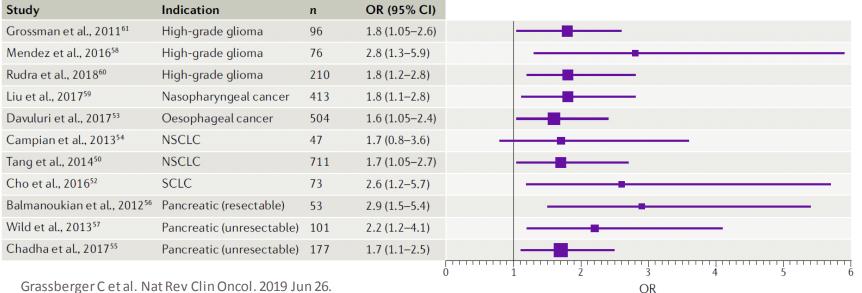
• 96 patients with GBM treated with RT + temozolomide + steroids, labs monitored for 1 year. CD4 count decreased and nadir at 2 months was prognostic for OS. Deaths overwhelmingly from cancer and not infection.



Grossman SA et al. Clin Cancer Res. 2011 Aug 15;17(16):5473-80.

Lymphopenia Is Bad

- Effect on OS by radiation-induced lymphopenia from published cohort studies
- OR>1 means inferior survival seen with lower lymphocyte counts



Grassberger C et al. Nat Rev Clin Oncol. 2019 Jun 26.

Less Lymphopenia with Protons

- 448 patients with esophageal cancer treated with chemoradiation
- Proton therapy associated with less lymphopenia

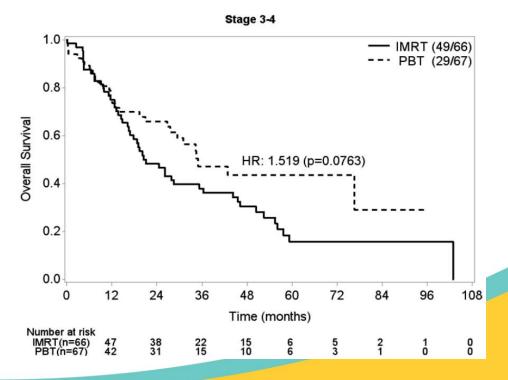
Fang P et al. Int J Part Ther. 2018 Winter;4(3):23-32.

Table 3. Comparison of propensity-matched patient, tumor, and treatment factors with and without grade 4 lymphopenia n = 220.

Characteristic	Grade 0-3 Lymphopenia (n = 134)	Grade 4 Lymphopenia (n = 86)	P value ^a
Age, mean (SD)	68.1 (9.1)	70.6 (7.7)	.03
PTV Volume (cm ³), mean (SD)	485 (225.61)	625 (256.48)	<.0001
Sex, No. (%)			.53
Female	28 (20.9)	15 (17.4)	
Male	106 (79.1)	71 (82.6)	
Stage, No. (%)			.57
1	6 (4.5)	4 (4.7)	
IIA	46 (34.3)	23 (26.7)	
IIB	6 (4.5)	2 (2.3)	
III	71 (53)	55 (64)	
IVA	5 (3.7)	2 (2.3)	
KPS, No. (%)			.40
70	11 (8.2)	10 (11.6)	
80-100	123 (91.8)	76 (88.4)	
Tumor location in esophagus, No. (%)			.02
Upper-middle	39 (29.1)	13 (15.1)	
Lower	95 (70.9)	73 (84.9)	
Induction chemotherapy, No. (%)			.72
No	98 (73.1)	61 (70.9)	
Yes	36 (26.9)	25 (29.1)	
Histology, No. (%)			.47
Adenocarcinoma	97 (72.4)	66 (76.7)	
Squamous cell carcinoma	37 (27.6)	20 (23.3)	
Radiation modality, No. (%)			.01
IMRT	58 (43.3)	52 (60.5)	
PBT	76 (56.7)	34 (39.5)	

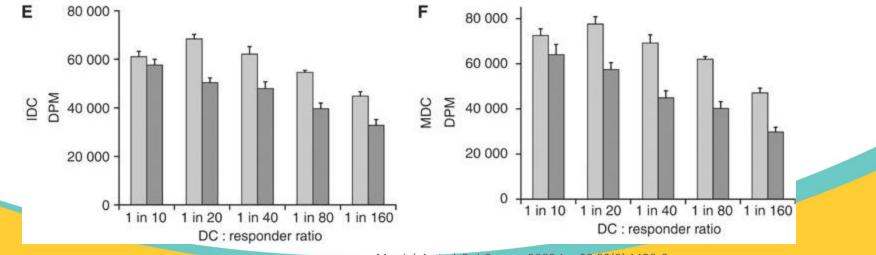
Protons = Less Lymphopenia = Better OS?

- Propensity score matching between IMRT and Protons (111 pts per arm). In stage 3-4 cancer, trend towards improved OS with protons than IMRT
- Univariate analysis showed PTV volume and lymphocyte reduction associated with OS



Beyond Lymphopenia

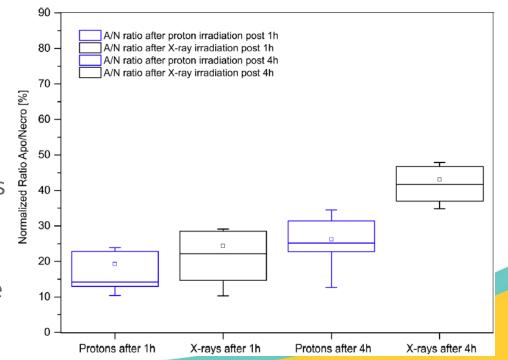
• Irradiated dendritic cells are less effective at priming lymphocytes, and produce less pro-inflammatory cytokines (IL-12) than unirradiated controls, while maintaining anti-inflammatory cytokine secretion (IL-10)



Merrick A et al. Br J Cancer. 2005 Apr 25;92(8):1450-8.

Are Protons More Immunogenic?

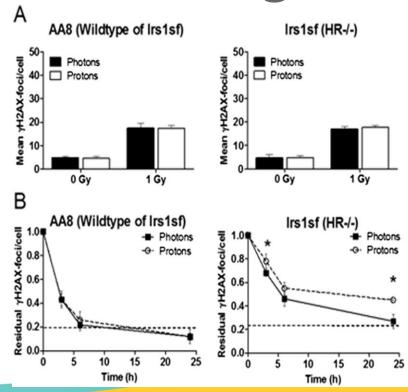
- Human peripheral blood lymphocytes treated with proton 60 MeV or 250 kVp Xrays to 4.0 Gy
- Apoptosis/necrosis ratio higher for x-rays than protons (protons kill more by necrosis)
- In general, necrosis is more immunogenic, involving release
 of molecules such as HMGB1



MiszczykClin Transl Radiat Oncol. 2018 Jan 31;9:23-29.

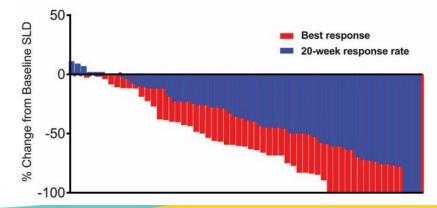
Different Types of DNA Damage

- Deficiency in Homologous Recombination Renders Mammalian Cells More Sensitive to Proton Versus Photon Irradiation
- Proton irradiation resulted in less repair of double strand DNA breaks than photon radiation in HR-deficient cells



Protons = More DNA Damage= More Neo-antigens

- = Better Response to Immunotherapy?
 - Genomes of mismatch repair-deficient tumors all harbor hundreds to thousands of somatic mutations
 - 86 patients with MMR deficiency across 12 tumor types. 53% objective response and 21% CR
 - Usual response rates
 - <5% complete response</p>
 - 20-30% objective response



Beyond Lymphopenia

Human P vs X CADPS2 CCL5 RSAD2 POF1B H19 SYTL4 CDYL2 PRKAA2 CMPK2 PAPL FCGR1A MMP13 AMTN FABP PDZD EPHA3 ADD2 AC147651.3 MEIS3 MMP9

- Tumors generated from cancer cells surviving multiple fractions of proton (P) or photon (X) radiation showed more aggressive phenotype post-X-irradiation
 - Proton radiated cells showed a downregulation of pro-angiogenic/pro-inflammatory genes, except for vegf-c, while most of these genes were upregulated after X irradiation
 - These observations suggest that P radiotherapy would lead to less pronounced lymphangiogenesis/metastasis

Lupu-Plesu Met al. Oncogenesis. 2017 Jul 3;6(7):e354.



Proving Value ...



Washington State Health Care Authority

WA HTA 2019 Review of Proton Therapy Coverage

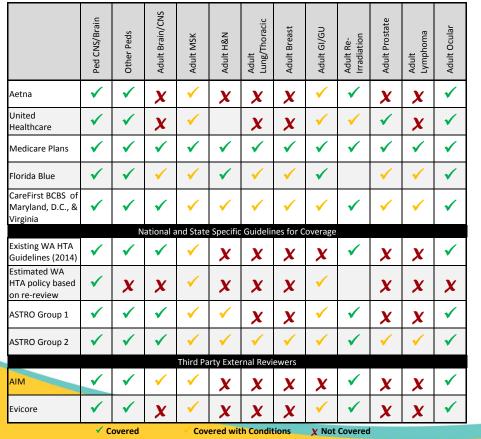
Washington State HTA

- Sets insurance coverage policy for Washington state employees and Medicaid beneficiaries
 - Includes all physicians at the Seattle Proton Center, who are employees of the University of Washington School of Medicine
 - Includes children covered by Medicaid
- Used by private insurers to guide coverage policy

Washington State HTA Timeline

- Announced intention to review proton therapy coverage in 2018
- Draft 311 page evidence report released 2/28/2019 by Aggregate Analytics, Inc.
- Written responses due April 1st
- Public hearing to provide comments May 17th

Coverage Variance Across the U.S.



- The evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country.
- Overly restrictive coverage policies can come with severe consequences to patients' health and to the financial well-being of insurers.

Washington State HTA

- Response efforts led by Dr. Ramesh Rengan and Annika Andrews
- Composed point-by-point written response
- Coordinated response with national organizations, and institutional leadership
- Dialog with HTA leadership, state leadership
- Invited external speakers:
 - Dr. Andrew Chang
 - Dr. William Hartsell
 - Dr. Sameer Keole
 - Dr. Steven Frank

Washington State HTA

- Proton therapy is NOT experimental
 - Over 150,000 patients treated worldwide
 - FDA Approved
 - Clear dosimetric advantage in many scenarios
- Radiation toxicity has a cost
 - H&N example (Dr. Steven Frank)
 - 50% decrease in feeding tube use with proton therapy
 - Patients treated entirely within UT system: treatment cost lower with proton therapy, likely due to lower toxicity rates

Washington State HTA-Response Points

- Evidence report conclusions out of step with national guidelines and coverage policy
- Long term care costs not considered
- Unreasonable standards for considering evidence
- Tougher standard for covering proton therapy (randomized trials) than other technologies and therapies

Our Commitment to Evidence Generation

- 2 registries (PCG registry, pediatric registry) >70% of the Center's patients have enrolled in the Proton Collaborative Group registry
- More than 25 open clinical trials
 - Breast
 - Brain
 - Prostate
 - Lung
 - Pediatric
 - Other cancers

Washington State HTA-Outcome

- Covered
 - All pediatric tumors
 - Adult cancers
 - Brain/spinal, ocular, base of skull
 - Head & Neck
 - Esophageal
 - Liver (HCC)
 - <u>Other cancers where other treatment options are</u> <u>contraindicated after review by a multi-d tumor board</u>
 - <u>NEW INDICATIONS COVERED</u>

Washington State HTA

- Additional feedback
 - More data expected
 - Long term outcomes
 - PCG registry expected to continue to produce long term outcomes for patients
 - Randomized trials

The Future

- Increasing acceptance of proton therapy
- Increasing availability of proton therapy
- Proving value
 - Less toxicity?
 - Better cancer control?
 - Beyond dosimetry
 - Biology of protons
 - Combination with systemic therapy



Thank you.