

# Skandionkliniken



## Current Clinical Evidence for Proton Therapy

**Valtakunnalliset onkologiapäivät 2013 Turussa.**

**Thomas Björk-Eriksson, senior consultant and associate professor  
Skandionkliniken and Sahlgrenska Academy  
Uppsala and Gothenburg  
SWEDEN**



# Current Clinical Evidence for Proton Therapy



- Background to the Skandionkliniken and describe the evidence level for PT in 2003-2005
- Overview of a number of publications on the evidence level for PT published during 2006-2013
- Present a small literature search and research on pros- and cons for PT in treatment of pediatric CNS and non-CNS tumours
- What is going on with PT in Sweden?
- Conclude the level of evidence for PT in 2013

# Current Clinical Evidence for Proton Therapy

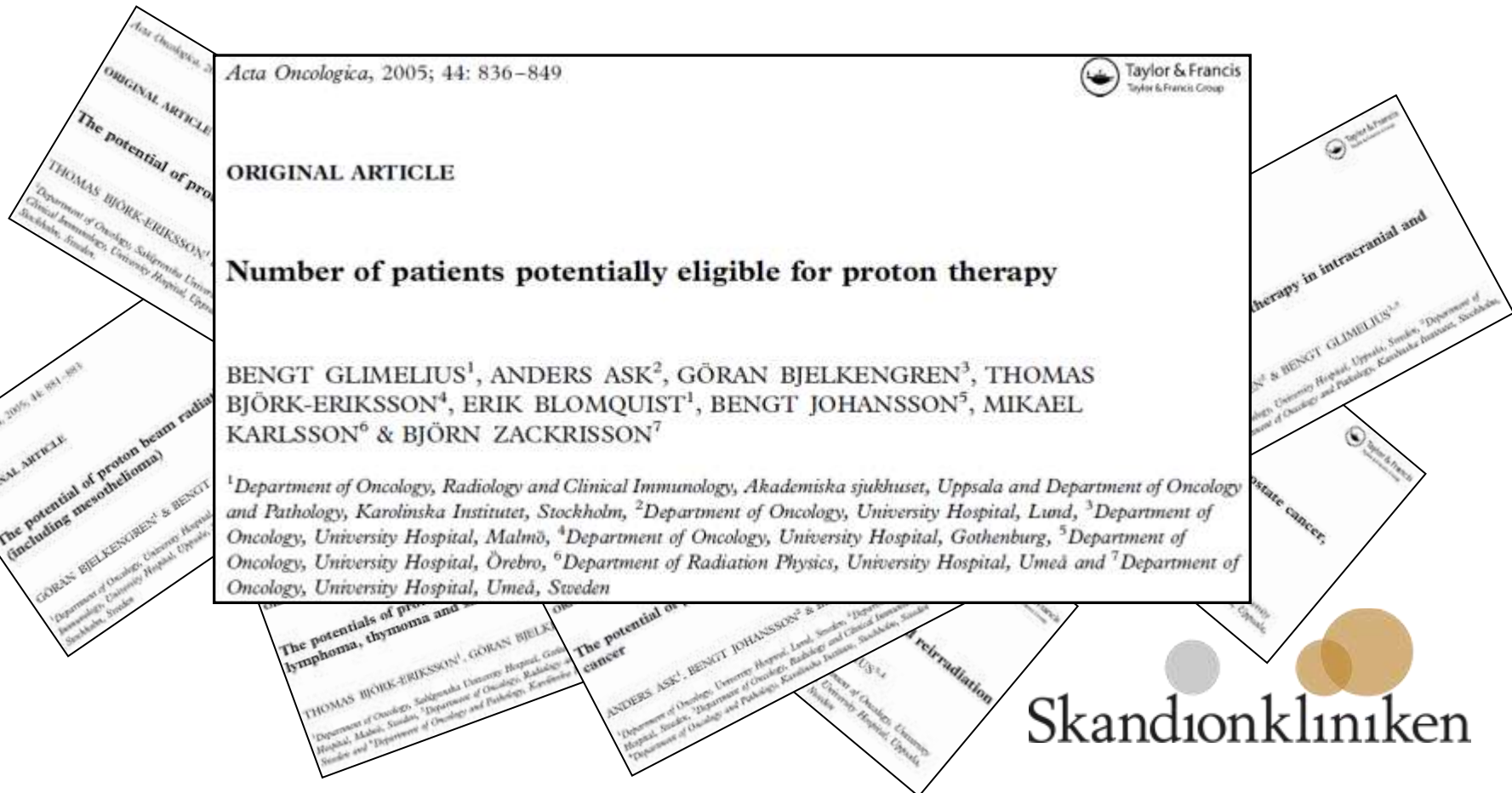
## Background

- Investigation from the Swedish Cancer Foundation (ACTA Oncol 2003;42(2):107-114); **"No doubt, proton therapy will become generally available for curative treatments within two decades"**
- January 2003 **SPTC-Svenskt protonterapicentrum** started
- October 2003 **Main Report** was published
  - ✓ Potential benefit for proton therapy in all different tumour types
  - ✓ Potential benefit for 2200-2500 (14-15%) of the patients presently irradiated (CNAO 16%, ETOILE 14.5% and MedAustron 13.5%)
  - ✓ Facility placed in Uppsala planned for 1000-2000 patients treated annually
  - ✓ Shared governance and distributed competence
  - ✓ Cost-effective
- January 2005 publication in Acta Oncologica of a Swedish expert-opinion based evaluation and estimation of the clinical need for proton therapy (PT)

# Current Clinical Evidence for Proton Therapy

## Background

- January 2005 publication in Acta Oncologica of a Swedish expert-opinion based evaluation and estimation of the clinical need for proton therapy



# Current Clinical Evidence for Proton Therapy

Table I. Estimate of the number of cases from Sweden eligible for proton beam therapy.

Tumour type <sup>1)</sup>	No. new cases in Sweden per annum	No. radiotherapy treatments in Sweden per annum <sup>2)</sup>	Suitable no. patients proton therapy
Intraocular melanoma	75	?	15
Skull-base chordoma/chondrosarcoma	30	?	20 – 25
Meningeoma	300	40	30 – 40
AVM	70	?	20 – 25
Medulloblastoma	30	30	20
Reirradiations			150 – 400
Paediatric cancer (not incl. medulloblastoma)	300		60 – 80
Pituitary adenoma	?		10 – 15
ENT cancer-nasopharynx/sinus	80		60
Sarcoma	375		40
ENT cancer-others	920	570	240
Oesophageal cancer	400	150	80
Rectal cancer	180	830	150
Breast cancer		3370	300
Thymoma		?	20
Lung cancer		485	350
Gynaecological cancer		650	50
Malignant gliomas	375	200	50 – 75
Cancer of the liver	400	70?	65 +
Mesothelioma	100	?	20
Prostate cancer	7800	1420	300
Malignant lymphomas	2000	460	20
Urinary bladder cancer	2300	180	?
Pancreatic cancer	800	50	50?
Gastric cancer	1100	70?	?
Palliations			90
	31 050	7650 <sup>3)</sup>	2220 – 2475 +

<sup>1)</sup> The tumour types are listed according to the support in favour of these treatments being given with protons in routine medical care (at the top) or that there are very good (middle) and good prospects (bottom), respectively, of clinical studies showing clinically relevant, “cost-effective” benefits.

<sup>2)</sup> The number of patients, according to the SBU survey, receiving external radiotherapy with a curative purpose in the diagnoses evaluated.

<sup>3)</sup> 9100 treatments were given to 7650 patients.

# Current Clinical Evidence for Proton Therapy

## Background

**Number of patients potentially eligible for proton therapy at SPTC was based upon;**

- Medline and Cochrane Library literature search on TCP/NTCP
- Clinical trials provided limited scientific information due to few trials, small number of patients, patient heterogeneity and early phases (phase I and II trials).
- More than 50 models studies demonstrating physical and biological aspects contributing to improved conformity index (CI), reduced doses to organs at risk (OAR) and reduced integral doses
- Despite major differences in methodologies comparing previous analysis (CNAO, ETOILE and MedAustron) same result (14-16%)
- Majority (80%) of patients suitable for proton therapy (2200-2500) should be treated within clinical prospective protocols

# Current Clinical Evidence for Proton Therapy

## Background

### *Evidence level in 2005*

Number of patients potentially eligible for proton therapy  
conclusions of the SPTC report ;

- Proton therapy is an *"established treatment"* for intraocular melanomas, skull-base chordomas/chondrosarcomas and meningiomas



# Current Clinical Evidence for Proton Therapy

Radiotherapy and Oncology 83 (2007) 123–132  
www.thegreenjournal.com



## Systematic review

### Proton therapy – A systematic review of clinical effectiveness

Dag Rune Olsen<sup>a,b,\*</sup>, Øyvind S. Bruland<sup>a,b</sup>, Gunilla Frykholm<sup>c</sup>, Inger Natvig Norderhaug<sup>d</sup>

<sup>a</sup>Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway, <sup>b</sup>University of Oslo, Norway, <sup>c</sup>St. Olavs Hospital, Trondheim, Norway,

<sup>d</sup>Norwegian Knowledge Centre for the Health Services, Oslo, Norway

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- "First systematic review assessing the clinical effectiveness of PT"
  - Literature search on Medline and Embase up to March 2006
  - Search terms; "proton\* and therapy and (cancer or carcinoma or malign\* or meningeoma\* or benign) not helicobacter"
  - Population – malignant or benign tumour disease
  - Intervention – proton irradiation
  - Outcomes – OS, LC, DFS, acute and late side effects and QoL
  - Study design – RCT, cohort- and case control trials, > 50 pats



# Current Clinical Evidence for Proton Therapy

Proton therapy – A systematic review of clinical effectiveness. Olsen D R, R&O 2007;83:123-132

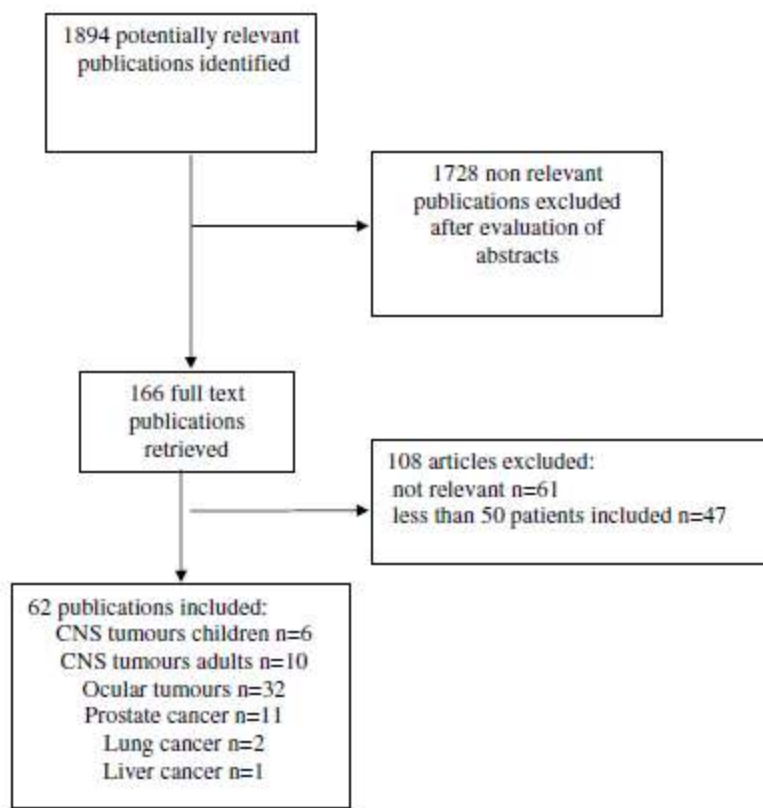


Fig. 1. Overview of the study selection procedure. Inclusion criteria were based on population, intervention, outcomes and study design.

## Results studies

- Four RCT (five publications)
- Five comparative studies
- Forty four case series
- RCT
  - prostate; two
  - ocular melanoma; one
  - chordoma/chondrosarcoma; one

# Current Clinical Evidence for Proton Therapy

Proton therapy – A systematic review of clinical effectiveness. Olsen D R, R&O 2007;83:123-132

## Results tumour sub-types

- Paediatric cranial tumours (n=6)
- Ocular melanomas (n=32)
- Chordomas and chondrosarcomas (n=10)
- Prostate cancer (n=11)
- NSCLC (n=2)
- Hepatocellular carcinoma (HCC) (n=1)

”**Conclusion:** The evidence on clinical efficacy of proton therapy relies to a large extent on non-controlled studies, and thus is associated with **low level of evidence** according to standard health technology assessment and evidence based medicine criteria.”

# Current Clinical Evidence for Proton Therapy

Radiotherapy and Oncology 83 (2007) 110–122  
www.thegreenjournal.com

## Systematic review

A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer

Mark Lodge<sup>a,\*</sup>, Madelon Pijls-Johannesma<sup>b</sup>, Lisa Stirk<sup>c</sup>, Alastair J. Munro<sup>d</sup>,  
Dirk De Ruyscher<sup>b,e</sup>, Tom Jefferson<sup>a</sup>

<sup>a</sup>Cochrane Cancer Network, Oxford, UK, <sup>b</sup>MAASTRO Clinic, Maastricht, The Netherlands, <sup>c</sup>Centre for Reviews & Dissemination, University of York, UK, <sup>d</sup>University of Dundee, Scotland, UK, <sup>e</sup>University Hospital Maastricht, GROW, MAASTRO Clinic, Maastricht, The Netherlands



- "First publication on detailed numerical data on the efficacy of modern particle therapy at a variety of tumour sites in a single publication"
- Literature search on eleven databases up to January 2006
- Search terms; "cancer\* or tumour\* .....proton therap\*; RBE"
- Handbook for Systematic Reviews of Interventions for trials
- Newcastle-Ottawa Scales (NOS) for non-randomised trials
- BMJ checklist for economic evaluations
- > 20 patients and follow up > two years

# Current Clinical Evidence for Proton Therapy

A systematic literature review of the clinical and cost effectiveness of hadron therapy in cancer. Lodge M, R&O 2007;83:110-122

Table 1

Results literature review in comparison with conventional therapy classified by tumour site

Tumour site	Protons		Ions	
	<i>n</i> studies/ <i>N</i>	Result	<i>n</i> studies/ <i>N</i>	Result
Head and neck	2/62	No firm conclusions	2/65	Similar to protons
ACC (locally advanced)	—	—	1/29	Superior
Prostate cancer	3/1751	Similar	4/201	No firm conclusions
Ocular tumours	10/7708	Superior	2/1343	Similar to protons
Gastro-intestinal cancer	5/369	No firm conclusions	2/73	No firm conclusions
Lung cancer (non-small cell)	3/156	No firm conclusions	3/205	Similar to SRT
CNS <sup>a</sup>	10/839	Similar	3/405	Similar to protons
Chordomas of skull base	3/302	Superior	2/107	Similar to protons
Sarcoma's	1/47	No firm conclusions	1/57	No firm conclusions
Pelvic tumours	3/80	No firm conclusions	2/49	No firm conclusions

Abbreviations: *N*, number of patients; ACC, adenoid cystic carcinomas; SRT, stereotactic radiotherapy.

<sup>a</sup> CNS, central nerve system tumours; inclusive skull base, spinal cord chondroma and chondrosarcomas.

$n_{\text{protons}}=40$ ,  $n_{\text{light ions}}=22$ , two randomised controlled trials in PT

# Current Clinical Evidence for Proton Therapy

A systematic literature review of the clinical and cost effectiveness of hadron therapy in cancer. Lodge M, R&O 2007;83:110-122

## **Conclusions:**

- Based on prospective and retrospective studies **proton irradiation** emerges as the treatment of choice for some **ocular melanomas (>4mm, posterior localized), skull base chordomas and chondrosarcomas**
- For prostate cancer treatment results with PT are comparable with best photon treatment
- No definitive conclusions on the relative merits of photons, protons and light ions can be drawn for head- & neck cancer, GI-tumours, NSCLC, sarcomas, cervical- and bladder cancer
- Further research into the clinical and cost-effectiveness of hadron therapy needed (13 papers assessed)
- European Hadron Therapy Register (EHTR) suggested

# Current Clinical Evidence for Proton Therapy

Radiotherapy and Oncology 103 (2012) 5–7



Systematic review

Charged particles in radiotherapy: A 5-year update of a systematic review

Dirk De Ruyscher<sup>a,\*</sup>, M. Mark Lodge<sup>b</sup>, Bleddyn Jones<sup>c</sup>, Michael Brada<sup>d</sup>, Alastair Munro<sup>e</sup>,  
Thomas Jefferson<sup>f</sup>, Madelon Pijls-Johannesma<sup>a</sup>

<sup>a</sup>Department of Radiation Oncology (MAASTRO), Maastricht University Medical Center, The Netherlands; <sup>b</sup>International Network for Cancer Treatment and Research, Oxford;

<sup>c</sup>Gray Institute for Radiation Oncology and Biology, University of Oxford; <sup>d</sup>Institute of Cancer Research, Sutton; <sup>e</sup>Department of Radiotherapy, University of Dundee, UK;

<sup>f</sup>Independent Epidemiologist, Rome, Italy

## **"Important issues":**

- No phase III trials during 2006-2010
- Not possible to conclude that protons or C-ions are truly superior to X-rays
- Need to break the vicious circle where lack of robust clinical data leads to a lack of evidence to support funding and further development of PT
- Global-, continental or national governance of PT

# Current Clinical Evidence for Proton Therapy

Radiotherapy and Oncology 83 (2007) 105–109  
www.thegreenjournal.com

*Editorial*

Proton beam therapy – Do we need the randomised trials and can we do them?

Bengt Glimelius<sup>a,b,\*</sup>, Anders Montelius<sup>a</sup>

<sup>a</sup>Department of Oncology, Radiology and Clinical Immunology, Uppsala University Hospital, Uppsala, Sweden, <sup>b</sup>Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden

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Reply on previous papers by Olsen D R et al and Lodge M et al (R&O 2007;83:110-122); ***”Why no clinical evidence for PT”***

- Better dose distributions in p+ than conventional beams
- Enables dose escalation in the tumour tissue
- Dose reduction in OAR:s
- Modern health care requires cost-effectiveness – demand for RCT
- Sub-groups of patients suitable for RCT must be identified with detectable gain within 3-5 years



# Current Clinical Evidence for Proton Therapy

VOLUME 25 • NUMBER 8 • MARCH 10 2007

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

## Proton Therapy in Clinical Practice: Current Clinical Evidence

*Michael Brada, Madelon Pijls-Johannesma, and Dirk De Ruyscher*

**Table 1.** Clinical Studies of Proton Therapy With at Least 20 Patients and With a Follow-Up Period of at Least 2 Years

Tumor Site	No. of Studies	No of Patients
Head and neck tumors <sup>15,75</sup>	2	62
Prostate cancer <sup>14,16,17</sup>	3	1,642
Ocular tumors <sup>18-26</sup>	9	9,522
Gastrointestinal cancer <sup>27-31</sup>	5	375
Lung cancer <sup>32-34</sup>	3	125
CNS tumors <sup>28-35,54,55</sup>	10	753
Sarcomas <sup>43</sup>	1	47
Other sites <sup>44-46</sup>	3	80
Total	36	12,606

- Systematic review using eleven different databases
- During the period 1993 - 2006
- Two phase III trials both in prostate cancer
- Mostly retrospective , "quasi-phase II trials"

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

## Proton Therapy in Clinical Practice: Current Clinical Evidence

*Michael Brada, Madelon Pijls-Johannesma, and Dirk De Ruyscher*

### ***"Results by tumour sub-types;"***

- Chordomas/chondrosarcomas of skull base – NSE for PT
- Ocular tumours – NSE for PT
- Prostate cancer – NSE for PT
- Head and neck cancer – NSE for PT
- Other tumours
  - ✓ Esophagus cancer – NSE for PT
  - ✓ HCC – NSE for PT
  - ✓ NSCLC – NSE for PT
  - ✓ Intracranial tumours – NSE for PT
  - ✓ Cervical- and bladder cancer – NSE for PT

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### ***"Results by tumour sub-types;"***

- Chordomas/chondrosarcomas – NSE for PT
- Ocular tumours – NSE for PT
- Prostate cancer – NSE for PT
- Head and neck cancer – NSE for PT
- Oropharyngeal cancer – NSE for PT
- Lung cancer – NSE for PT
- Breast cancer – NSE for PT
- Gliomas – NSE for PT
- Intracranial tumours – NSE for PT
- Cervical- and bladder cancer – NSE for PT

**PT introduced on the clinical arena by enthusiasm for particle therapy, belief in its benefit and considerable financial outlay!  
Need for evidence-based medicine!!!**

# Current Clinical Evidence for Proton Therapy

VOLUME 25 • NUMBER 8 • MARCH 10 2007

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

## Particle Radiation Therapy Using Proton and Heavier Ion Beams

*Daniela Schulz-Ertmer and Hirohiko Tsujii*

### **"Important issues":**

- Uveal melanomas, pediatric tumours, skull base and intracranial tumours, prostate, lung, HCC, H&N-tumours, bone tumours and other malignant and benign tumours were commented upon.
- Scientific evidence that PT is superior to conventional photon RT in uveal melanomas
- "PT is indicated in pediatric tumours because of reduced risk of SM"
- Reduced scientific evidence in favor for skull base chordomas /chondrosarcomas and malignant and atypical meningiomas
- Role for PT in the other tumour types remains unclear

# Current Clinical Evidence for Proton Therapy

VOLUME 26 • NUMBER 2 • JANUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

## Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

Michael Goitein, Department of Radiation Oncology, Harvard Medical School, Boston, MA

James D. Cox, Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

### **”Why are there almost no RCT comparing PT and x-ray therapy?”:**

- Depth dose characteristics – treatment planning studies!
- No difference in tissue response per unit dose between protons and x-rays – large body of in vivo and vitro evidence!
- Radiation to normal tissue damage just as it does to tumours – documented in countless clinical reports over many decades!
- Can anyone avoid to conclude that there is, at very least, a high probability that protons can provide superior therapy to x-rays?
- There would not be equipoise between the proton- and x-ray arms!

# Current Clinical Evidence for Proton Therapy

Radiotherapy and Oncology 103 (2012) 8–11



Systematic review

An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee

Aaron M. Allen<sup>a,\*</sup>, Todd Pawlicki<sup>b</sup>, Lei Dong<sup>c</sup>, Eugene Fourkal<sup>d</sup>, Mark Buyyounouski<sup>d</sup>, Keith Cengel<sup>e</sup>, John Plastaras<sup>e</sup>, Mary K. Bucci<sup>c</sup>, Torunn I. Yock<sup>f</sup>, Luisa Bonilla<sup>a</sup>, Robert Price<sup>d</sup>, Eleanor E. Harris<sup>g</sup>, Andre A. Konski<sup>h</sup>

<sup>a</sup>Davidoff Center, Tel Aviv University, Israel; <sup>b</sup>University of California, San Diego, La Jolla, USA; <sup>c</sup>M.D. Anderson Cancer Center, University of Texas, Houston, USA; <sup>d</sup>Fox Chase Cancer Center, Philadelphia, USA; <sup>e</sup>University of Pennsylvania, Philadelphia, USA; <sup>f</sup>Massachusetts General Hospital, Boston, USA; <sup>g</sup>H. Lee Moffitt Cancer Center, Tampa, USA; <sup>h</sup>Wayne State University Medical Center, Detroit, USA

Keynote Lecture; Dr Aaron Allen

ASTRO's report on the evidence for PT in clinical radiotherapy – has the ground become more solid? PTCOG 52, Essen, Thursday, 6 June 2013.

***Two questions remain;***

- Is PT better than current standard of care with photon treatment?
- Should PT be adopted as the standard care?

# Current Clinical Evidence for Proton Therapy

An evidence based review of proton beam therapy: The report of  
ASTRO's emerging technology committee by Aaron Allen et al  
R&O 2012;103:8-11

## ***Review focusing on the use of PT to treat;***

- CNS malignancies – SE for a benefit of PT in skull base chordomas
- Lung cancer – NSE for PT
- GI-malignancies – HCC perhaps benefit for PT, otherwise NSE for PT
- Ocular melanomas – SE for a benefit of PT in large ocular melanomas
- Prostate cancer – PT is an option but no clear benefit over IMRT
- Head- & neck cancer – NSE for PT
- Pediatric malignancies – CNS tumours rational to use PT but clinical evidence is lacking, NSE for PT in non-CNS pediatric malignancies



# Current Clinical Evidence for Proton Therapy

An evidence based review of proton beam therapy: The report of  
ASTRO's emerging technology committee by Aaron Allen et al  
R&O 2012;103:8-11

## *Review focusing on the use of PBT to treat;*

- CNS malignancies – SE for a benefit of PT in gliomas, meningiomas, chordomas
- Lung cancer – NSE for PT
- GI-malignancies – HCC perhar, otherwise NSE for PT
- Ocular melanomas – SE for PT in large ocular melanomas
- Prostate cancer – PT but no clear benefit over IMRT
- Head- & neck – SE for PT
- Pediatric malignancies – CNS tumours rational to use PT but clinical evidence lacking, NSE for PT in non-CNS pediatric malignancies

**"There is reason to be optimistic about the potential developments in PT"**

# Current Clinical Evidence for Proton Therapy



Seminars in  
**RADIATION  
ONCOLOGY**

## Controversies in Clinical Trials in Proton Radiotherapy: The Present and the Future

Robert C. Miller, MD, MS,<sup>\*,†</sup> Mark Lodge,<sup>‡</sup> Mohammad Hassan Murad, MD, MPH,<sup>§</sup> and Bleddyn Jones, MA, MSc, MD<sup>¶</sup>

*... "the lack of prospective clinical trials"*

- Physical and biological characteristics of charged particles
- Clinical equipoise
- Low risk for systemic failure
- High risk for local progression
- High risk of toxicity with conventional therapy
- Taking care of the caution of  $RBE=1.1$  for p+



Skandionkliniken

# Current Clinical Evidence for Proton Therapy



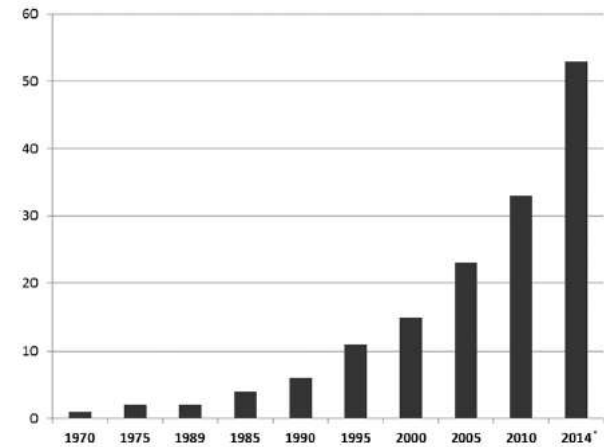
Seminars in  
**RADIATION  
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Robert C. Miller, MD, MS,<sup>\*,†</sup> Mark Lodge,<sup>‡</sup> Mohammad Hassan Murad, MD, MPH,<sup>§</sup> and  
Bleddyn Jones, MA, MSc, MD<sup>¶</sup>

### ***Between Lodge M (2007) - De Ruyscher D publications in (2012);***

- Fifty four percent increase in operating CPT centers between 2005 (25) and 2011 (39)
- No significant improvement of the level of clinical evidence for PT 2005-2011
- >100 prospective trials on [ClinicalTrials.gov](http://ClinicalTrials.gov)
- Importance of observational studies for long term results



**Figure 1** Global growth in particle therapy centers (\*projected value including planned centers).

# Current Clinical Evidence for Proton Therapy



Seminars in  
**RADIATION  
ONCOLOGY**

## Clinical Controversies: Proton Therapy for Prostate Cancer

Kent W. Mouw, MD, PhD,\* Alexei Trofimov, PhD,<sup>†</sup> Anthony L. Zietman, MD,<sup>†</sup> and  
Jason A. Efstathiou, MD, DPhil<sup>†</sup>

### *Current and Evolving Evidence;*

Photon and PT effective, toxicity profile well-defined still unclear if one modality is superior to the other!

- Much hope to NCT01617161 study comparing PT and IMRT low/intermediate prostate cancer (79Gy(RBE), <http://clinicaltrials.gov/ct2show/NCT01617161>)



# Current Clinical Evidence for Proton Therapy



Seminars in  
**RADIATION  
ONCOLOGY**

## Clinical Controversies: Proton Radiation Therapy for Brain and Skull Base Tumors

Stephanie E. Combs, MD,\* Normand Laperriere, MD,<sup>†</sup> and Michael Brada, FRCP, FRCR, DSc<sup>‡</sup>

***Same kind of literature search as Olsen DR and Lodge M (R&O, 2007);***

- Forty one publications of clinical studies selected
- Patient number >20, follow up  $\geq$  12 months
- Glioma (n=7), meningioma (n=8), acoustic neuroma (n=5), pituitary adenoma (n=2), low- and high grade glioma (n=3), chordoma and chondrosarcoma (n=7)
- No advantage of PT over more conventional modern photon techniques in any of the tumour types



# Current Clinical Evidence for Proton Therapy



Seminars in  
**RADIATION  
ONCOLOGY**

## Clinical Controversies: Proton Therapy for Thoracic Tumors

Dirk De Ruyscher, MD, PhD,\* and Joe Y. Chang, MD, PhD<sup>†</sup>

### *Why PT in NSCLC?*

- Potential need for dose escalation in vicinity of vital OAR:s
- Passive-scattering solution for problems with mobile targets
- Ongoing randomised trials in advanced NSCLC e g NCT00915005, IGART vs. IGAPT (74 Gy and 74 and 66 CGE)+ concurrent CHT
- Published results on PT in NSCLC no clear superiority over photons



# Current Clinical Evidence for Proton Therapy

## Literature search on Pediatric PT; pros- and cons.

The screenshot shows a PubMed search results page for the query "pediatric proton therapy". The search was performed on May 13, 2013, and returned 415 results. The results are sorted by "Recently Added" and displayed in a list format. The first five results are visible, each with a checkbox, a title, authors, journal, date, and PMID. The results include studies on proton pump inhibitors, intracranial tumors, gastroesophageal reflux, proton therapy and radiation sensitivity, and standard fractionation for diffuse choroidal hemangiomas. The page also shows filters for article types, availability, and publication dates.

pediatric proton therapy - PubMed - NCBI

PubMed  
Sign in to NCBI

Search  
Advanced search

Display Settings: Summary, 100 per page, Sorted by Recently Added

Results: 1 to 100 of 415

Page 1 of 5

Filters: MeSH Filters

PMC Images search for pediatric proton therapy

Article types

Clinical Trial  
Review  
More...

Text availability

Abstract available  
Free full text available  
Full text available

Publication date

5 years  
10 years  
Custom range...

Species

Humans  
Other Animals

Clear all

Show additional filters

1. **Proton Pump Inhibitor Therapy in Chemotherapy-Induced Protonemia.**  
Fettah A, Yazici N, Bayram C, Kincaloglu CT, Tunc B.  
J Pediatr Hematol Oncol. 2013 May 3. [Epub ahead of print] No abstract available.  
PMID: 23552814 [Published - as supplied by publisher]  
Related citations

2. **Diffuse Intracranial Tumors of nonneuroepithelial germ cell etiology: diagnostic and therapeutic implications.**  
Aker AA, Sethi RV, Hackley-Whyle ET, Elm D, Tarbell NJ, York TL, MacDonald SM.  
Neuro Oncol. 2013 May 7. [Epub ahead of print]  
PMID: 23848532 [Published - as supplied by publisher]  
Related citations

3. **Gastroesophageal reflux: management guidelines for the pediatrician.**  
Lightdale JR, Gremse DA; SECTION ON GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION.  
Pediatrics. 2013 May;131(5):e1894-95. doi: 10.1594/peds.2013-0421. Epub 2013 Apr 26.  
PMID: 23838110 [Published - in process]  
Related citations

4. **Proton Therapy and Radiation Sensitivity in Dyskeratosis Congenita.**  
Hartman RL, Hill-Kayser CE.  
J Pediatr Hematol Oncol. 2013 Apr 24. [Epub ahead of print]  
PMID: 23919122 [Published - as supplied by publisher]  
Related citations

5. **Standard fractionation low-dose proton radiotherapy for diffuse choroidal hemangiomas in pediatric Sturge-Weber syndrome.**  
Yonemura Y, MacDonald SM, Shidekrot Y, Mukai S.  
J AAOO. 2013 Apr 23. doi: 10.1093/jao/13.0000000000000000. Epub ahead of print.  
PMID: 23918830 [Published - as supplied by publisher]  
Related citations

6. **Acute Toxicity of Proton Beam Radiation for Pediatric Central Nervous System Malignancies.**  
Sunjara G, Poonu PD, Hill-Kayser C, Lustig RA.  
Pediatr Blood Cancer. 2013 Apr 22. doi: 10.1002/pbc.24584. [Epub ahead of print]  
PMID: 23918811 [Published - as supplied by publisher]  
Related citations

Find related data  
Database: Gen  
Search details  
Recent activity

http://www.ncbi.nlm.nih.gov/pubmed/2013-05-13-13-27-00

## Pediatric proton therapy

MeSH-terms;

("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields]) AND ("proton therapy"[MeSH Terms] OR ("proton"[All Fields] AND "therapy"[All Fields]) OR "proton therapy"[All Fields])

415 potentially relevant publications, 56 relevant abstracts (1992-2013) assessed regarding pros- and cons in pediatric PT.

- Clinical- and dose planning studies (3D-CRT, IMRT, 3D-CPT och IMPT)
- Small number of cases
- Heterogeneous diagnoses
- No randomised clinical studies



# Current Clinical Evidence for Proton Therapy

## Pros ("potential") in pediatric PT;

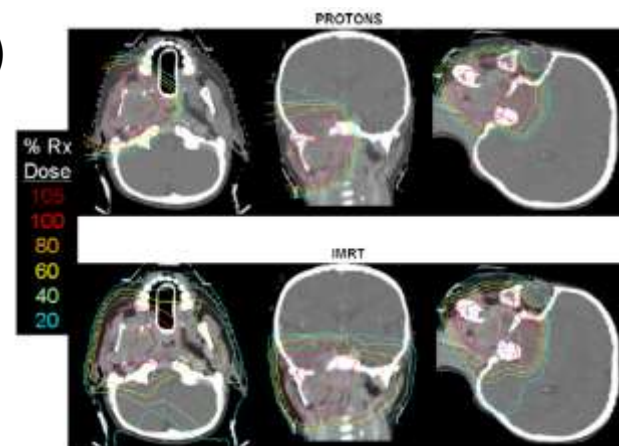
- Feasible, safe and "effective" form of radiation therapy
- Good target dose coverage not at least in vicinity of OAR:s
- Reduced dose to the normal tissue (small, large and complex target volumes)
  - Reduced acute toxicity
  - Reduced late toxicity (growth retardation, neuro-cognitive-, endocrine-, heart-, lung-, sight-, hearing-, bone marrow-, breast- and kidney-)
- Dose escalation possible (brain tumours and sarcomas)
- Intensified chemotherapy possible
- "Cost-effective" treatment (medulloblastoma)
- Reduced risk of secondary cancer

# Current Clinical Evidence for Proton Therapy

## Cons ("potential") in pediatric PT ;

- All traditional adverse effects after radiation therapy
  - Acute (erythema, headache and fatigue)
  - Subacute (pseudo progression after CNS irradiation)
  - Late (endocrine-, CVL, secondary cancer)
- Risk of asymmetric growth retardation →
- Secondary neutron formation (secondary cancer)
- Differences in radiobiological and physical characteristics of p+ (RBE, penumbra etc)
- Dose distribution sensitive for changes in target- and normal tissue volumes and movements

3D-CPT och IMRT av PMRMS.

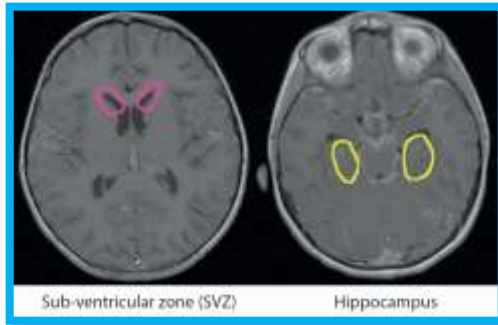


Kozak K, Adams J, Krejcarek S et al. A dosimetric comparison of proton and intensity-modulated photon radiotherapy for pediatric parameningeal rhabdomyosarcomas. IJROBP. 2009; 74(1): 179-186.

# Current Clinical Evidence for Proton Therapy

## Neurocognitive adverse effects following craniospinal irradiation (CSI) for medulloblastoma (MB)

Neurogenic niches (CT/MRT)

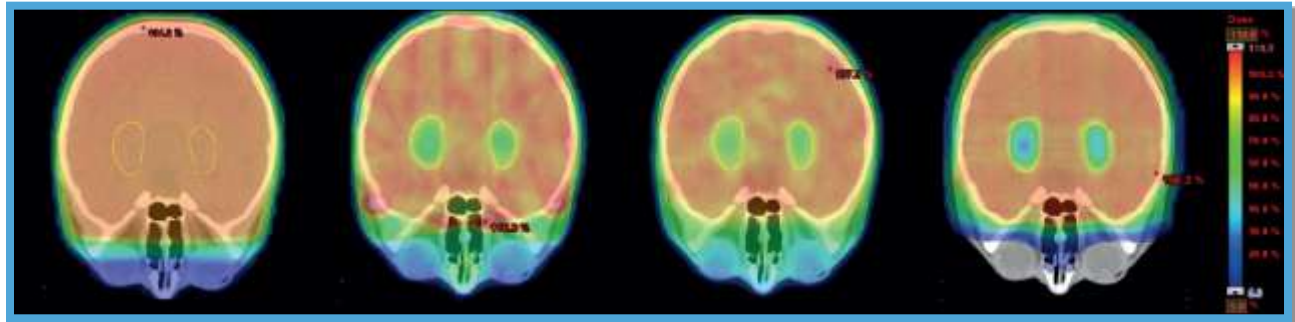


3D-RT

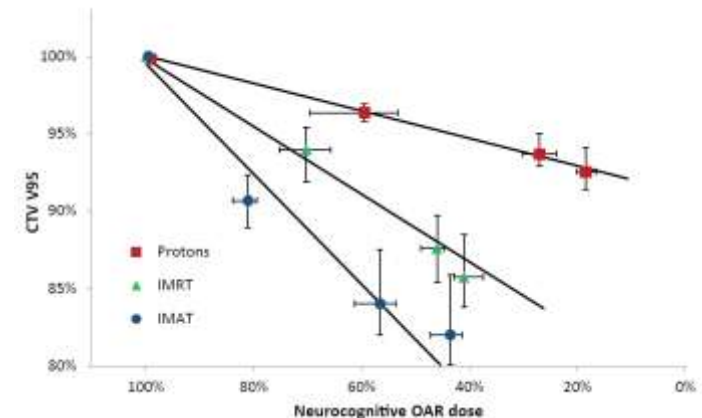
IMRT

IMAT

IMPT



- 3D-CRT = "Conventional" radiation therapy
- IMRT = intensity modulated radiation therapy (OAR dose 80%)
- IMAT = intensity modulated arc therapy (OAR dose 90%)
- IMPT = intensity modulated proton therapy (OAR dose 40%)



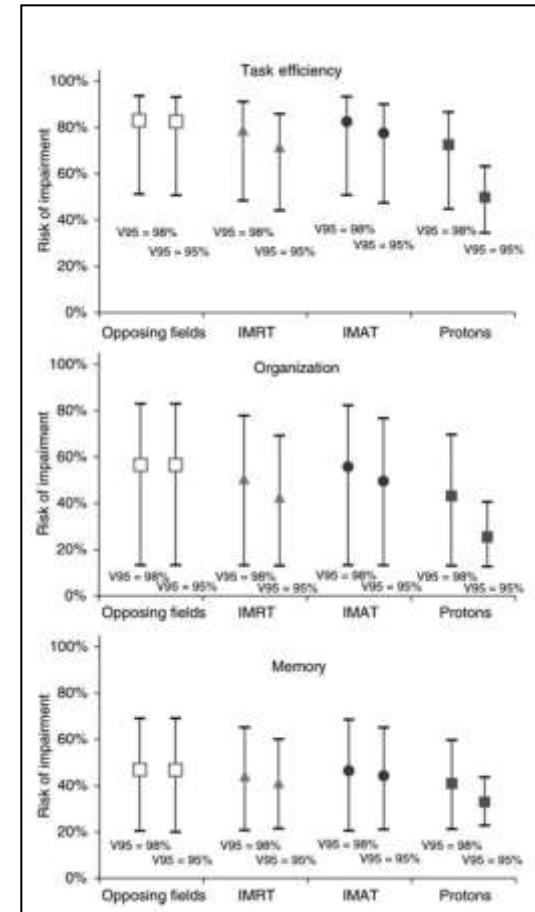
Malin Blomstrand, N. Patrik Brodin, Per Munck af Rosenschöld et al. Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma. *Neuro Oncol.* 2012 Jul;14(7):882-9.

# Current Clinical Evidence for Proton Therapy

## Neurocognitive effects following CSI of MB

### **Conclusions;**

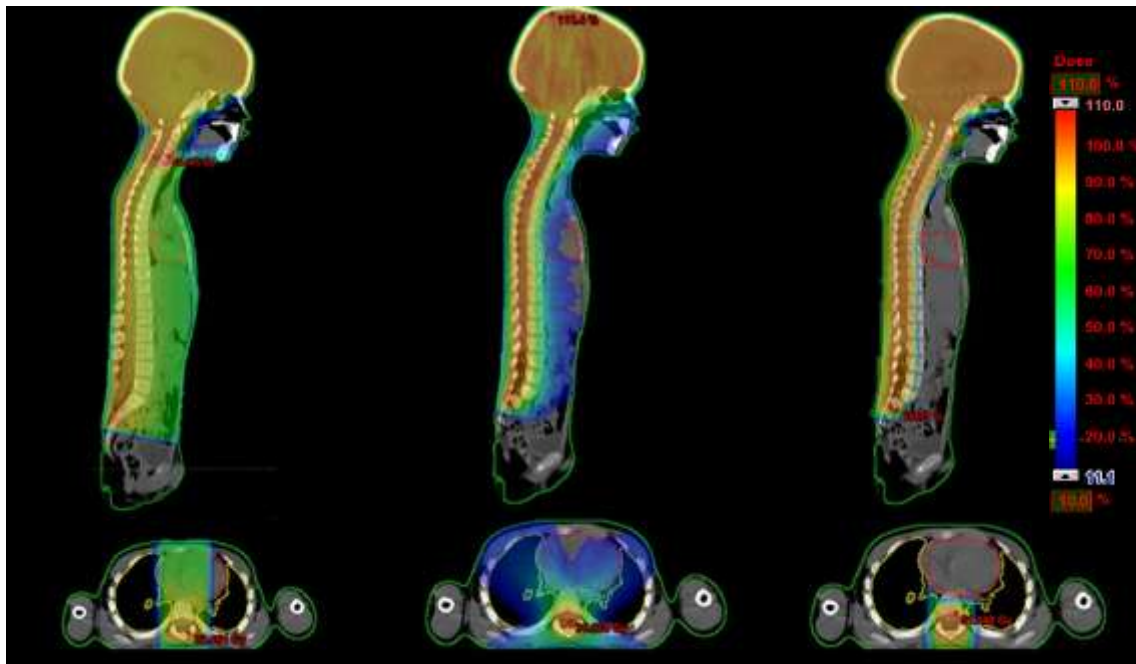
- Possible to reduce the dose to OAR: (hippocampus and SVZ) in CSI for MB with potentially reduced neurocognitive adverse effects.
- IMPT most effective radiation therapy technique to reduce the dose to the neurogenic niches
- Need for clinical trials!



Malin Blomstrand, N. Patrik Brodin, Per Munck af Rosenschöld et al. Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma. *Neuro Oncol.* 2012 Jul;14(7):882-9.

# Current Clinical Evidence for Proton Therapy

Risk of solid secondary cancer after CSI of childhood MB



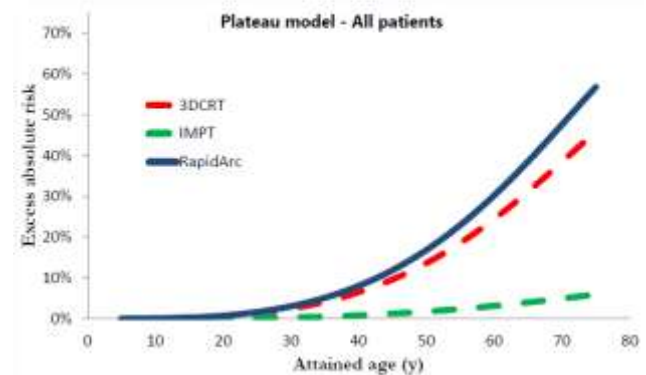
3D-CRT

RapidArc

IMPT

Brodin P, Munck af Rosenschöld P, Aznar M et al. Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. Acta oncol, 2011; 50: 806-816.

Risk of solid secondary cancer



# Current Clinical Evidence for Proton Therapy

Summary of recommended design of clinical studies;

- Helsinki declaration article 6 provides support for CRT in PT
- Prospective phase II trials of best available technique and/or adequately powered phase III trials reporting agreed endpoints of clinical relevance – LC, DFS, OS, QoL, toxicity etc.
- PT in one experimental arm compared with control arm without protons alternatively PT as a boost or different proton dose levels
- Clinical equipoise, low risk of systemic failure or manageable distant disease, high risk of local progression and/or high risk of toxicity with conventional therapy

# Current Clinical Evidence for Proton Therapy

## What is going on in PT Sweden?

- A number of experienced clinicians/scientists responsible national groups for writing treatment/research protocols in a number of different tumour types;

Per Bergström/Petra Witt  
Mats Perman/B Glimelius  
Kristina Nilsson  
Jan Nyman  
Björn Zackrisson  
Per Malmström/Petra Witt  
Bengt Tholander  
M Agrup och A Widmark  
Christina Goldkuhl  
Karin Ahlberg

CNS  
GI  
Pediatric  
Lungcancer  
H&N  
Breast cancer  
Gynecological cancers  
Prostate cancer  
Hodgkin´s disease  
Caring science



# Current Clinical Evidence for Proton Therapy

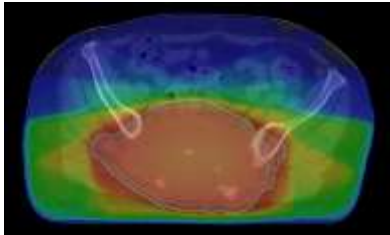
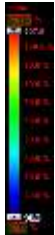
Based on a number of recent publications on PT it is concluded that;

- Large increase in proton therapy centers but no corresponding increase in clinical evidence for PT during 2005-2013
- In ocular melanomas and skull base chordomas there is evidence for a benefit of PT over photon therapy
- In HCC, meningiomas and prostate cancer there is evidence for efficacy of PT but not superior to that of photon therapy
- In pediatric CNS malignancies PT appears to be superior to photon therapy but more data are needed
- No evidence for PT in the treatment of lung-, H&N-, GI-, brain- and pediatric non-CNS malignancies
- There is optimism about more RCT in the future! Yesterday almost 200 studies on PT at [ClinicalTrials.gov](https://clinicaltrials.gov)

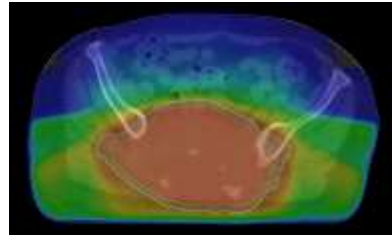
# Current Clinical Evidence for Proton Therapy

Kiitos teidän mielenkiinnostanne!

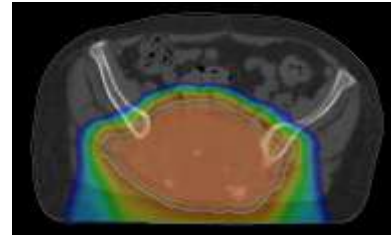
Thank you for your attention!



3D-CRT



IMRT



SFUD PT



Randomisation

STOP