

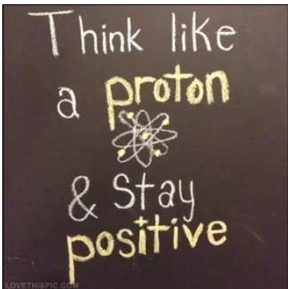


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kankernetwerk  
Radiotherapie  
Medische Oncologie  
Hematologie

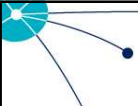



What is there left to gain with Proton / Particle therapy?

Prof. Dr. Dirk Verellen

D. Verellen has a scientific collaboration with: RaySearch Lab, SunNuclear, SIT, ORFIT, DoseVue



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## Outline

- What's the fuzz all about?
  - Why would (should) we invest in p<sup>+</sup>?
  - The basics: difference between photons and protons
- How do we accelerate p<sup>+</sup>?
- How do we deliver p<sup>+</sup>?
- What are the challenges?


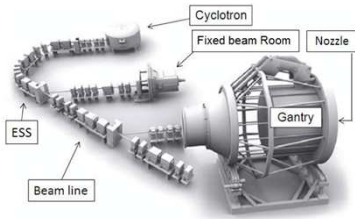



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## About photons and p<sup>+</sup>

- Photon therapy reached its pinnacle of development ...
- Protons are at the start of ascent ...





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## Believers and non-believers

- Wise words from a wise man:



**When men are most sure and arrogant they are commonly most mistaken,** giving views to passion without that proper deliberation which alone can secure them from the grossest absurdities.

— *David Hume*

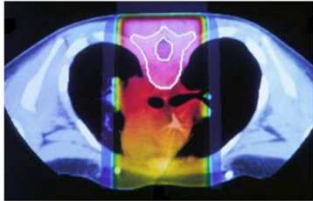
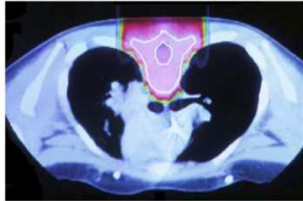
AZ QUOTES

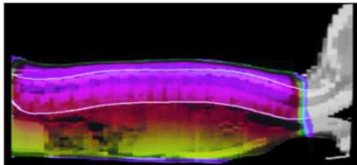
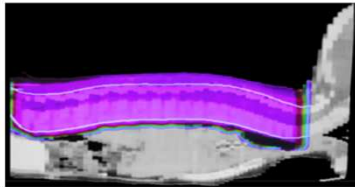
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### What's the fuzz all about?

- Photon therapy
- Proton therapy

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### What's the fuzz all about?

- 5 most frequent cancers in men and women:

<p>Prostate Lung Colon &amp; rectum Bladder Stomach, NHL</p>		<p>Breast Colon &amp; rectum Uterus Lung Ovary</p>
--	---	--

These cancers are **NOT** "targeted" in the Belgian Hadron Project

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## What's the fuzz all about?

- Main indication for protons ...
- Pediatric oncology!

	2000	2001	2003
leukemia	85	108	90
lymphoma	39	43	34
embryonal t.	52	54	63
CNS	94	68	65
bone	15	18	24
STS	35	34	35
<b>TOTAL</b>	<b>320</b>	<b>325</b>	<b>313</b>

Medulloblastoma in a 5-year old child  
Protons vs 4 MV photons

- Potential recruitment in Belgium: ~ 100 cases/year

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## About photons and protons ...

**MATTER**      **FORCE**

u c t      γ g

d s b      W Z

Quarks      Gauge Bosons

ν<sub>e</sub> ν<sub>μ</sub> ν<sub>τ</sub>      H

e μ τ      Higgs Boson?

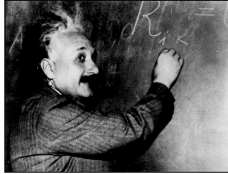
Leptons

THE STANDARD MODEL OF PARTICLES AND FORCES  
IS THIS ALL THAT EXISTS?

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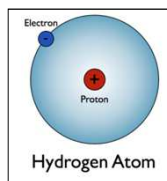
## About photons and protons ...

- What is a photon?



- Quantum (particle) of light
- Constant speed in vacuum
- No charge
- No (rest) mass

- What is a proton?

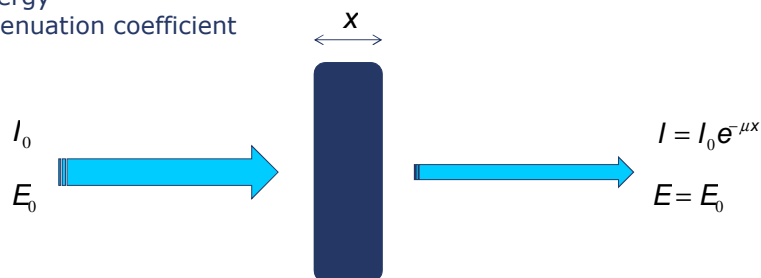


- Hydrogen atom without  $e^-$
- Can be stopped
- Elementary positive charge
- 2000 times the mass of an  $e^-$

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## Interaction of photons with matter

$I$ : Intensity  
 $E$ : Energy  
 $\mu$ : attenuation coefficient

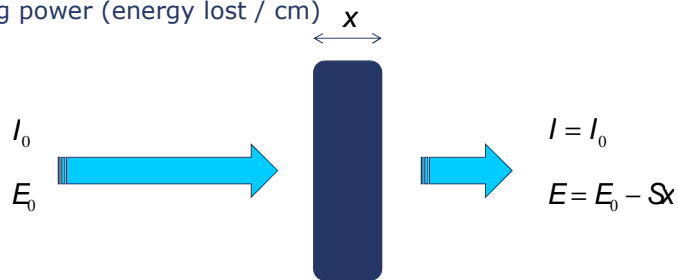


- The particle either "**leaves**" the beam or is **unchanged**
- The beam is **attenuated**

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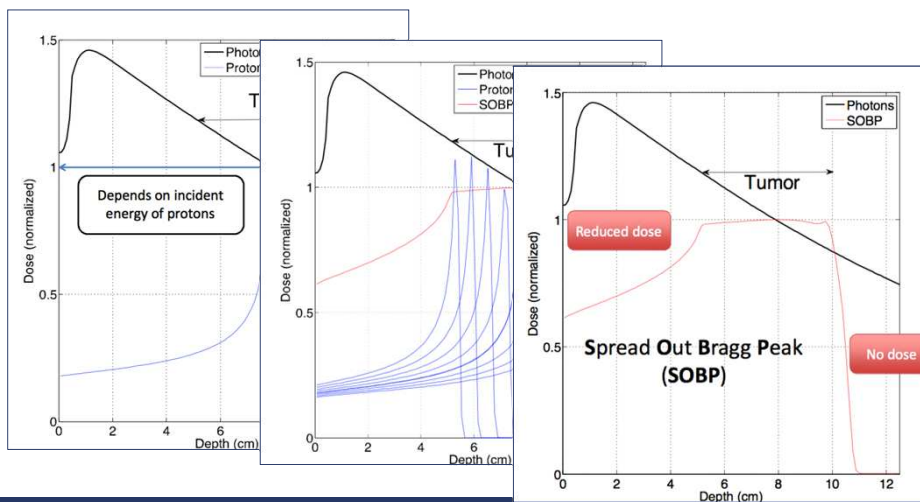
## Interaction of protons with matter

$I$ : Intensity  
 $E$ : Energy  
 $\mu$ : ~~attenuation coefficient~~  
 $S$ : stopping power (energy lost / cm)



- The particle **slows down**

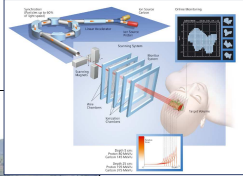

## About photons and protons ...



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## How do we accelerate protons?

- Synchrotrons





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Paul Scherrer Institute

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## How do we accelerate protons?

- Cyclotrons




Yves Jongen

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## So, let's keep it simple



**iPhone 6s**

**VS**



**Galaxy S7**


\$808.95 as of Apr. 22nd	PRICE	\$741.16 as of Apr. 21nd
750 x 1334	RESOLUTION	1440 x 2560
4.7 inches	SCREEN SIZE	5.5 inches
64 GB	STORAGE	32 GB
2 GB	RAM	4 GB
1715 mah	BATTERY	3600 mah
5.04 ounces	WEIGHT	5.54 ounces

<http://www.productchart.com/smartphones/>
VENNGAGE

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## A simple comparison



**versus**

Integral dose
Conformity
3D-4D IGRT
Robust dose distribution sensitivity to anatomical variations
<i>In vivo</i> dosimetry
Clinical evidence
Cost per patient
<b>Routine</b>

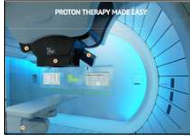


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## A simple comparison



<b>versus</b>
<b>Integral dose</b>
<b>Conformity</b>
<b>3D-4D IGRT</b>
<b>Robust dose distribution</b> sensitivity to anatomical variations
<b><i>In vivo</i> dosimetry</b>
<b>Clinical evidence</b>
<b>Cost per patient</b>
<b>Routine</b>



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## Integral dose and low dose wash




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## A simple comparison



**versus**


	<b>Integral dose</b>	👎
	<b>Conformity</b>	
	<b>3D-4D IGRT</b>	
	<b>Robust dose distribution</b> sensitivity to anatomical variations	
	<b><i>In vivo</i> dosimetry</b>	
	<b>Clinical evidence</b>	
	<b>Cost per patient</b>	
	<b>Routine</b>	



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## A simple comparison





**versus**

	<b>Integral dose</b>	👎
	<b>Conformity</b>	
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	<b>Routine</b>	



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## Protons always better than photons?

Stuschke et al. *Radiation Oncology* 2013, **8**:93  
<http://www.ro-journal.com/content/8/1/93>

### Re-irradiation of recurrent head and neck carcinomas: comparison of robust intensity modulated proton therapy treatment plans with helical tomotherapy

Martin Stuschke<sup>1,2\*</sup>, Andreas Kaiser<sup>2</sup>, Jehad Abu-Jawad<sup>1</sup>, Christoph Pöttgen<sup>1</sup>, Sabine Levegrün<sup>1</sup>  
 and Jonathan Farr<sup>2,1</sup>

**Abstract**

**Background:** To test the hypothesis that the therapeutic ratio of intensity-modulated photon therapy using helical tomotherapy (HT) for retreatment of head and neck carcinomas can be improved by robust intensity-modulated proton therapy (IMPT).

**Methods:** Comparative dose planning with robust IMPT was performed for 7 patients retreated with HT.



**Results:** On average, HT yielded dose gradients steeper in a distance  $\leq 7.5$  mm outside the target ( $p < 0.0001$ , F-test) and more conformal high dose regions down to the 50% isodose than IMPT. Both methods proved comparably robust against setup errors of up to 2 mm, and normal tissue exposure was satisfactory. The mean body dose was smaller with IMPT.

**Conclusions:** IMPT was found not to be uniformly superior to HT and the steeper average dose fall-off around the target volume is an argument pro HT under the methodological implementations used. However, looking at single organs at risk, the normal tissue sparing of IMPT can surpass tomotherapy for an individual patient. Therefore, comparative dose planning is recommended, if both methods are available.

**Keywords:** IMPT, intensity modulated proton therapy, Robust optimization, Robustness, Plan comparison, Re-irradiation, Helical tomotherapy.

**IMPT** was found **NOT** to be uniformly superior to HT and the steeper average dose fall-off around the target volume is an argument pro HT

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## Protons always better than photons?

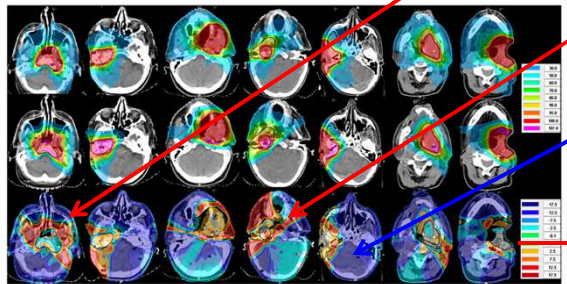
Stuschke et al. *Radiation Oncology* 2013, **8**:93  
<http://www.ro-journal.com/content/8/1/93>

- "red shell" around CTV: HT more conformal

HT

IMPT

Dose difference IMPT-HT



- heterogeneities  
- scatter

low dose wash


p<sup>+</sup> lower
p<sup>+</sup> higher

**Figure 1 Dose distribution.** Dose distributions for patients 1-7 from left to right. Helical tomotherapy (HT) and intensity modulated proton therapy (IMPT) plans are shown in row 1 and row 2. Corresponding dose difference plots (IMPT minus HT) are given in the third row for the respective patients.


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## A simple comparison




	<b>versus</b>	
👍	<b>Integral dose</b>	👎
👍	<b>Conformity</b>	👍
	<b>3D-4D IGRT</b>	
	<b>Robust dose distribution</b> sensitivity to anatomical variations	
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	Clinical evidence	
	Cost per patient	
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## A simple comparison



	<b>versus</b>	
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### Why IGRT?



Verellen et al.  
Nature Reviews Cancer, 2007

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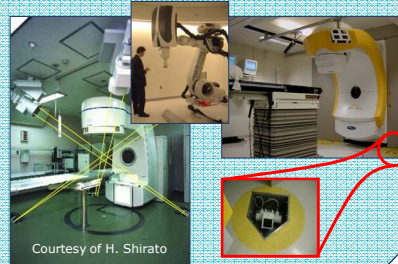
### Image-guided radiotherapy



On-board volumetric imaging



On-board planar imaging




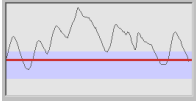
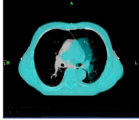
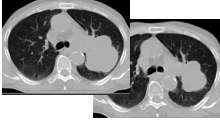
Courtesy of H. Shirato

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### Adaptive radiotherapy ...

- With radiotherapy we **are exploring** the concept ART

Seconds	Minutes	Days	Weeks
<ul style="list-style-type: none"> <li>• Breathing</li> <li>• Peristaltic</li> <li>• Heart Beat</li> </ul> 	<ul style="list-style-type: none"> <li>• Patient motion</li> <li>• Tumor drifts</li> </ul> 	<ul style="list-style-type: none"> <li>• Breathing pattern</li> <li>• Baseline shifts</li> <li>• Patient position</li> </ul> 	<ul style="list-style-type: none"> <li>• Shrinkage</li> <li>• Progression</li> <li>• Weight loss</li> </ul> 

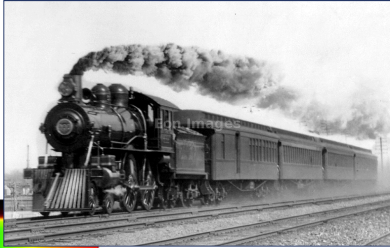
- With **protons** ART is **NECESSARY!!!!**

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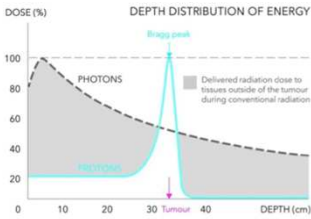
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### The key message from p<sup>+</sup> therapy

- It's a heavy particle, the "Bragg peak" stops

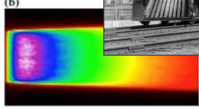


(a) DOSE (%) vs DEPTH (cm) - DEPTH DISTRIBUTION OF ENERGY

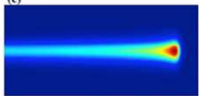


PHOTONS (grey area), PROTONS (red line), Bragg peak (red arrow), Tumour (red arrow), Delivered radiation dose to tissues outside of the tumour during conventional radiation (grey area)

(b) Heatmap showing dose distribution for photons, showing a broad area of high dose.



(c) Heatmap showing dose distribution for protons, showing a sharp peak of high dose at the tumor location.



Dinh JQ, Translational Cancer Res, 2012

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## The key message from p<sup>+</sup> therapy

- ... the Bragg peak stops ...
- but we don't always know where!!

Knopf&Lomax, PMB, 2013

The diagram shows three scenarios: (i) nominal situation, (ii) "uncertain" situation, and (iii) "uncertain" situation. It compares photon, proton (Bragg Peak), and proton (SOBP) beams. A red box highlights "Few %" and another red box highlights "From 0% to 100%".

Originally planned dose distribution vs. Dose recalculation on modified CT. Includes Day 0 and Day 35 scans showing tumor regression.

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Montparnasse, 1895

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## Adapting to volumetric changes

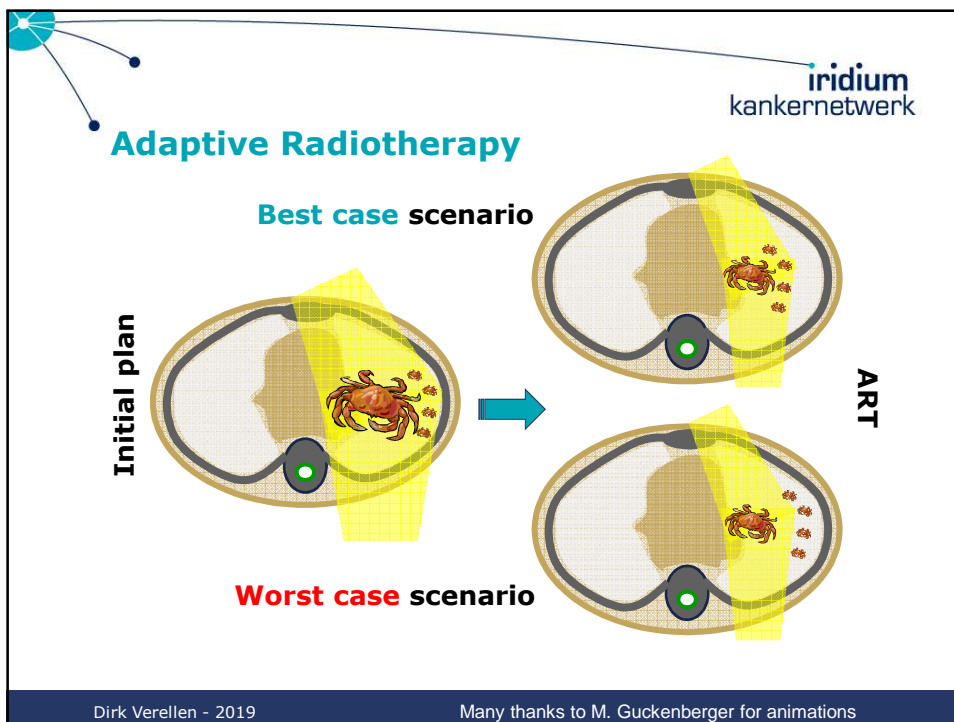
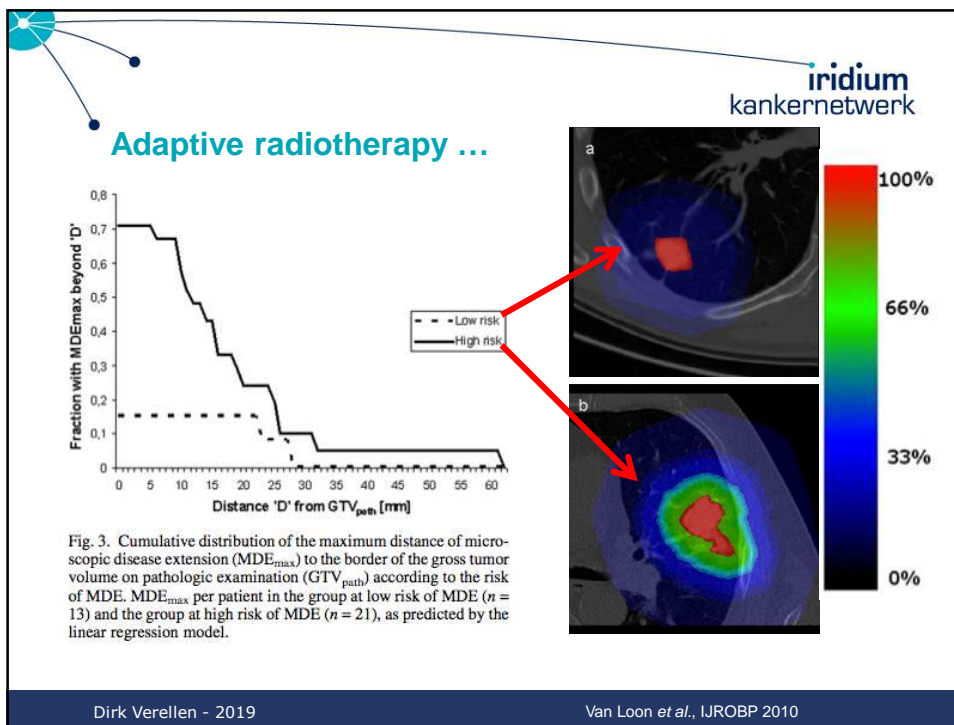
Plan
Week 2
Week 3
Week 4
Week 5
Week 6

Initial plan

Adaptive plan

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Many thanks to M. Guckenberger for animations







## Consensus paper, 2017

- Particle Therapy Co-Operative Group (PTCOG), Thoracic and Lymphoma Subcommittee:


International Journal of  
Radiation Oncology  
biology • physics  
www.redjournal.org

Critical Review

### Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee

Joe Y. Chang, MD, PhD,\* Xiaodong Zhang, PhD,\* Antje Knopf, PhD,† Heng Li, PhD,\* Shinichiro Mori, PhD,‡ Lei Dong, PhD,§ Hsiao-Ming Lu, PhD,¶ Wei Liu, PhD,¶ Shahed N. Badiyan, MD,# Stephen Both, PhD,\*\* Arturs Meijers, MS,† Liyong Lin, PhD,†† Stella Flampouri, PhD,‡‡ Zuofeng Li, DSc,‡‡ Kikuo Umegaki, PhD,§§ Charles B. Simone, II, MD,# and Xiaorong R. Zhu, PhD\*


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## Consensus paper, 2017

- Robustness, motion management, interplay effect:
  - Range uncertainty (HU, S)
  - Intrafractional organ motion (respiration, peristalsis, ...)
  - Anatomical changes (opening airways, fluid accumulation, ...)
  - Concept of safety margin useless (beam-specific PTV? Most people already have problems to define institution-specific PTV margins)
  - “potentially manifesting as extreme local tumor underdosage or normal structure overdosage”
  - “most pronounced when PBS-PT is delivered in a limited number of fractions” ...

D'OH! Are we going back to conventional fractionation?




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## Robust ... based on 4D-CT?

- And another thing:



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## Robust ... based on 4D-CT?


- The so-called 4D CT is nothing but a **continuous movie-loop** and might NOT be representative for the breathing pattern at the time of treatment!!!!

Real-time  
Fluoroscopy  
during treatment

4D-CT  
Amplitude-based  
binning



Dhont J., Verellen D. (Radiother Oncol, 2018)

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## Consensus paper, 2017

- **Motion management and robust optimization** and evaluation are **crucial** for minimizing uncertainties associated with beam range and organ motion.
- In any event, if the dosimetric criteria are met, the patient can be treated with PBS-PT; **otherwise, PBS-PT should not be offered.**
- Tony (Lomax) even introduced the "worst-case robustness approach" ... **If the plan is not robust, then the plan should be optimized** ...

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## Robust planning

It seems a bit awkward that the strength of proton treatment needs to be reduced to compensate for the fact that particle treatment is unforgiving for density uncertainties and anatomical variations, whereas **photons by nature are more robust and forgiving** for these issues in real-life clinical situations, thoracic lesions are a case in point.

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## A simple comparison

		<b>versus</b>		
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## A simple comparison

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## Automate or perish

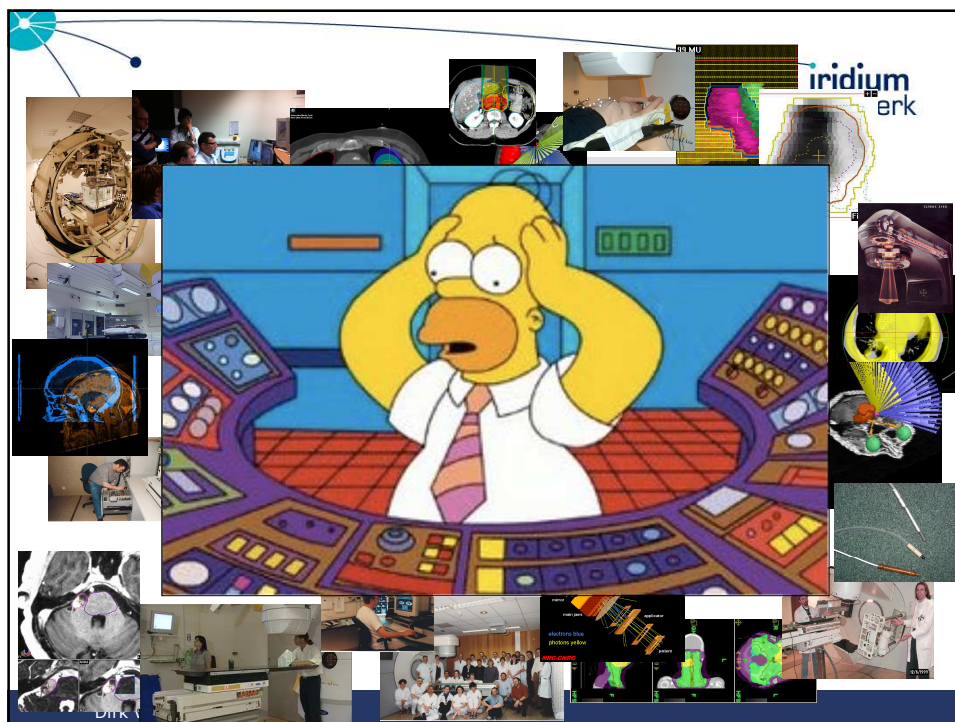
● ELECTRONIC POSTER  
**Physics track: Dose measurement and dose calculation**

> 1-year experience with automated transit *in vivo* dosimetry in a busy multicenter Department  
*E. Bossuyt (Belgium), R. Weytjens, S. De Vos, R. Gysemans, D. Verellen* EP-1728

- *In vivo* dosimetry
- safety, quality
- Standardization and automation
  - Continuous, individualized patient QA
  - Dose tracking
  - Trending
  - Big data















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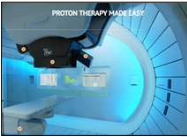











## A simple comparison

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## A simple comparison

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## Clinical evidence

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## Clinical evidence

- Health Technology Assessment and Systematic review reports
- Belgian Health Care Knowledge Centre (**KCE, 2007**)
- Belgian Health Care Knowledge Centre (**KCE, 2019**)

**3.2 Systematic reviews and HTA reports**

In total, 11 systematic reviews / HTA reports were included (Table 2). Three systematic reviews focused on one cancer type, i.e. two reviews on hepatocellular cancer<sup>1,2</sup> and one review on glioblastoma cancer.<sup>3</sup> All other systematic reviews and all HTA reports had no limitations in scope regarding the clinical indications. Three HTA reports were (mainly) an overview of reviews.<sup>4, 5, 6</sup> Unfortunately, these were also the most recent HTA reports. As a result, recently published primary studies were not captured by these reviews and HTAs.

The most recent HTA report was published by CADTH.<sup>6</sup> The literature search was of good quality and was run in June 2017. The report focused on systematic reviews, results were presented narratively. In general, the authors concluded that in most cancer types the clinical effectiveness of proton treatment, alone or in combination with photon radiotherapy, is comparable to other types of radiotherapy. INESSS also published a HTA report that mainly focused on secondary literature and data extraction process). In RHTA, published a HTA report (description of included studies) for high-quality comparative studies. QUERI published a HTA report systematic reviews and compar ICER published a HTA report, 1 February 2014. The search was lack of data on the cost-effective Dionisi et al. focused their search appraisal, English literature only and the experimental character and was of good quality. The a

### Key points

- Proton beam therapy can represent an indication for rare and specific tumours in selected groups of patients where conventional therapy presents a significant risk for fragile structures in the vicinity. The quality of actual evidence is nevertheless poor and further research is thus needed.
- Carbon ion therapy is an appealing but still experimental approach.















Patel et al. focused their search on glioblastoma cancer.<sup>3</sup> The search was run in April 2014, and was of good quality. The authors performed a meta-analysis, that was done using correct methods when looking at the individual treatments. However, when comparing the different types of radiotherapy, baseline risk was taken into account by adjusting for tumour stage only. For the meta-analysis a total of 41 non-comparative observational studies (43 cohorts) was used, including 20 cohorts treated with photon therapy and 10 cohorts treated with proton treatment (NB: also other types of charged particle therapy were included, and some cohorts received combinations of treatment). Overall survival at the longest follow-up did not differ significantly between proton treatment and IMRT (RR = 1.02; 95%CI 0.77-1.35, p = 0.89), nor did the 5-year overall survival (RR = 1.39; 95%CI 0.99-1.94, p = 0.057). In addition, disease-free survival at the longest follow-up did not differ significantly between proton treatment and IMRT (RR = 0.96; 95%CI 0.40-2.42, p = 0.97). However, the 5-year disease-free survival was significantly better in the proton group (RR = 1.93; 95%CI 1.36-2.75, p = 0.003). Also locoregional control at the longest follow-up was significantly better in the proton group (RR = 1.18; 95%CI 1.01-1.37, p = 0.031), but the 5-year locoregional control did not differ significantly (RR = 1.06; 95%CI 0.68-1.67, p = 0.79).

The reports and/or reviews published by KCE,<sup>4</sup> Lodge et al.,<sup>5</sup> and Dionisi et al.,<sup>6</sup> all dated from 2007, and did not add new information to the above.

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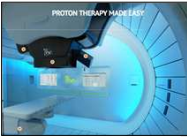













## A simple comparison

		<b>versus</b>		
		<b>Integral dose</b>		
		<b>Conformity</b>		
		<b>3D-4D IGRT</b>		
		<b>Robust dose distribution</b> sensitivity to anatomical variations		
		<b>In vivo dosimetry</b>		
		<b>Clinical evidence</b>		
		<b>Cost per patient</b>		
		<b>Routine</b>		

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## Halperin's rule

- Most tumours are radioresistant if you miss them ...

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## Halperin's rule (cont'd)

- Most tumours are radioresistant if you miss them ...
- Protons may offer many **new** and **expensive** ways of missing the tumour

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## ... and society pays



**CAN WE AFFORD THE WAR ON CANCER?**

Immunotherapy vaccines could extend survival in a handful of cancers. But personalizing treatment, payers argue, is not sustainable. Where should the line be drawn?

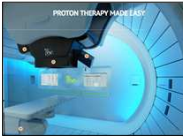














**BY TED SILVERMAN**

Two years ago, the U.S. Food and Drug Administration took a step that some thought would never occur — it approved the approval of a personalized cancer vaccine. The vaccine, known as sipuleucel-T, is a personalized vaccine made from a patient's own immune cells with a recombinant antigen. The personalized product is then infused back into the patient, allowing the immune system to target and attack the cancer. The "personalized" vaccine is the most recent successful

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## A simple comparison

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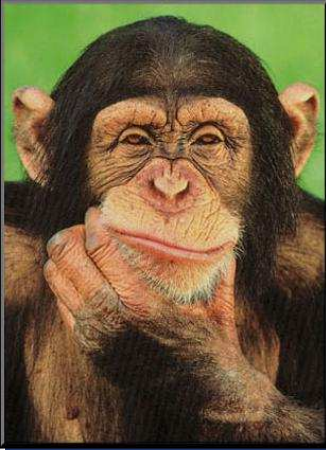
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## A simple comparison



PROTON THERAPY MADE EASY



**Routine**



👍👍👎👎👎👎👎👎


👎👍👍👍👍👍👍👍

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## Believers and non-believers

- From Hume to Feynman
- The idea is to try and give all the information to help others to judge the value of your contribution; not just the information that leads to judgment in one particular direction or another
  - Richard P. Feynman



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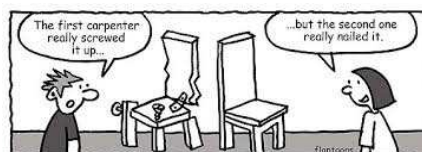
## Conclusions

- The goal of treatment is to “cure” the cancer, or prolong survival in patients with advanced disease, while preserving the highest possible quality of life in both the long and short term.
- A debate whether or not protons are superior to photons is a **CATEGORY MISTAKE**

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## Conclusions cont'd

- Radiotherapy is a highly dynamic and evolving discipline, crucial for treatment of cancer and it features different specialties each with their typical applications:
  - External beam and brachytherapy
  - Photons, electrons, p+, other particles, ...



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## Challenges in radiation oncology

- The most important thing to a patient **is not** the availability of some high technology device, rather **it is** the ability of a team of physicians, physicists, dosimetrists and therapists to use a technology with skill for the benefit of the patient.
  - Dr. Marc Edwards
- The **true challenge** is to develop the wisdom to know when to select which treatment modality in the clinic.
  - Dr. Steve Webb



L'expérience cruciale, F. Schuiten