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European Organisation for Research and Treatment of Cancer
The future of cancer therapy

The need for randomized controlled trials in particle therapy: which are the specific challenges in technology assessment trials and the role of EORTC

Geneva
July the 3rd, 2019

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Overview

- EORTC?
- Clinical trials for Technology assessment
- Potential pitfalls
- How to address them?

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EORTC by the numbers (2018)

A world-class network	An expert HQ	Unique output
• 2770 patients screened 2412 patients enrolled in Clinical Trials • > 5,300 collaborators • 933 institutions • 37 countries • 19 active groups & task-forces • 118 collaborative groups • 76 peer reviewed papers	• 219 employees • > 200,000 patients in database • ± 27,000 patients in follow-up • 10 EORTC HQ peer reviewed papers	• **213 ongoing studies:** ○ 57 studies open to patients ○ 11 studies open in 2018 • **52 studies in development:** ○ 26 studies in protocol outline development ○ 15 studies in protocol development ○ 11 studies in regulatory activation

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EORTC Mission

AIM: To increase cancer patients' survival and quality of life

- **Generating robust medical evidence**: design, coordinate and conduct **multidisciplinary**, **clinical and translational** trials, leading to therapeutic progress and new standard of treatment in care

- **Setting Standards**: being a **reference** for methodological research and an **authority** in establishing the standards of treatment in care

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EORTC is unique

Independent	• **Not for Profit organization** where research is done with **unwavering independence** and accountability for making all results public
Multidisciplinary	• Our research spans **all aspects of cancer management**: medical, radiation, surgical, imaging, and translational research
Multi-tumour	• Network of **over 5.300 oncology experts**. Our research is solution-driven, for all types of cancers, leaving no-one behind
International	• A network of **over 930 institutions** in **37 countries;** coordinated and managed from headquarters in Brussels with over **200 core staff**
Regulatory compliance	• Our experts ensure our activities meet the **strictest regulatory standards and quality assurance requirements**

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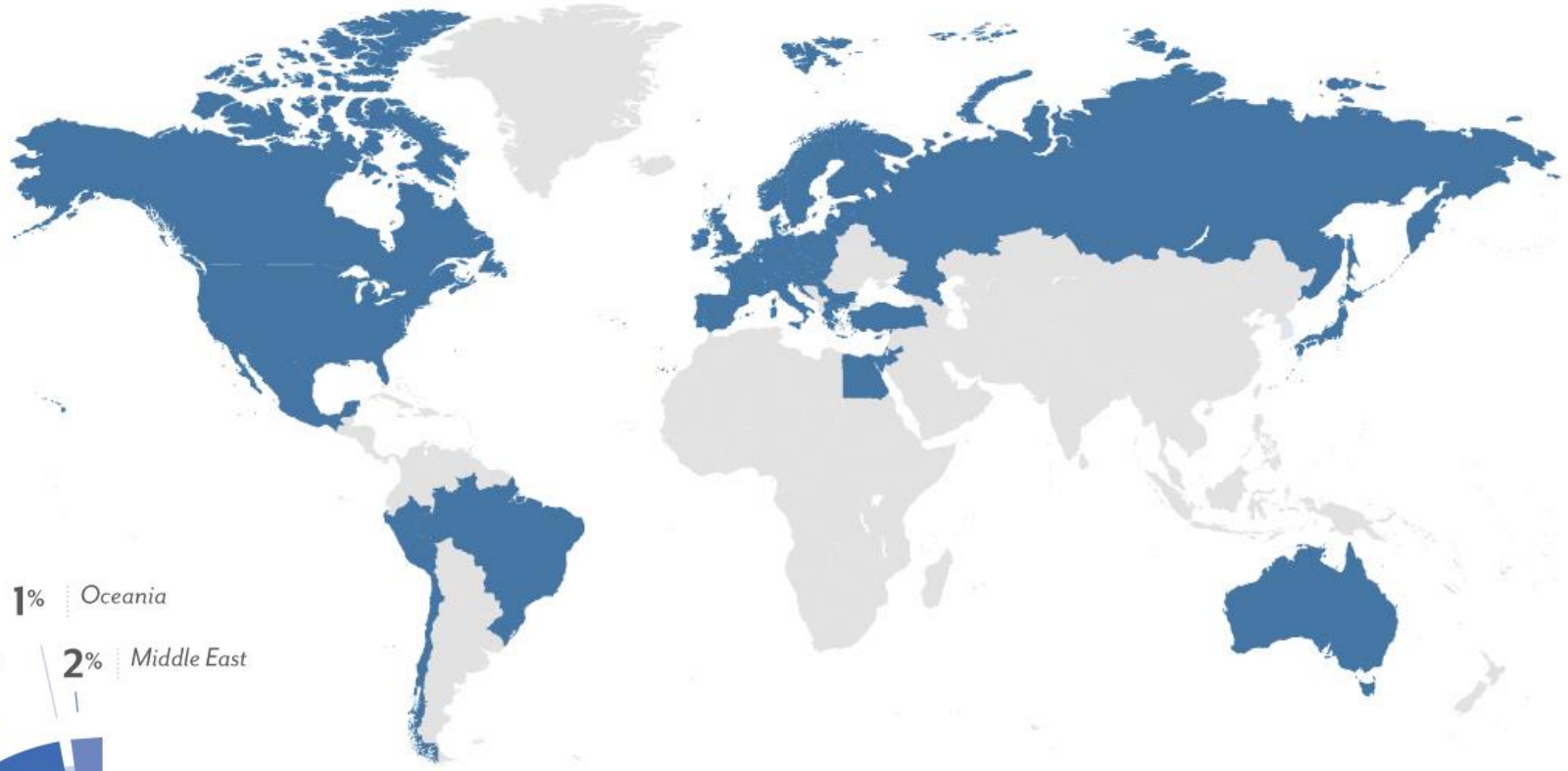
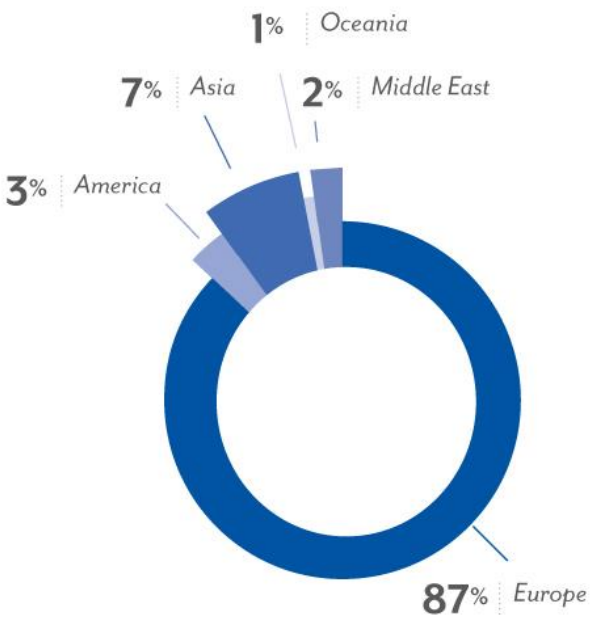
EORTC's International Presence





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Particle therapy assesment

… or really [insert tech name here] assessment

Clinical trials 101

- Phase I
  - Dose escalation
- Phase II: safety and efficacy
  - Single arm, or
  - Two arm randomized (inform future phase III)
- Phase III: superiority or non-inferiority
  - Common pitfalls to all tech assesment trials
- Phase IV: long term cost-effectiveness (QALY etc)

Level 1 evidence

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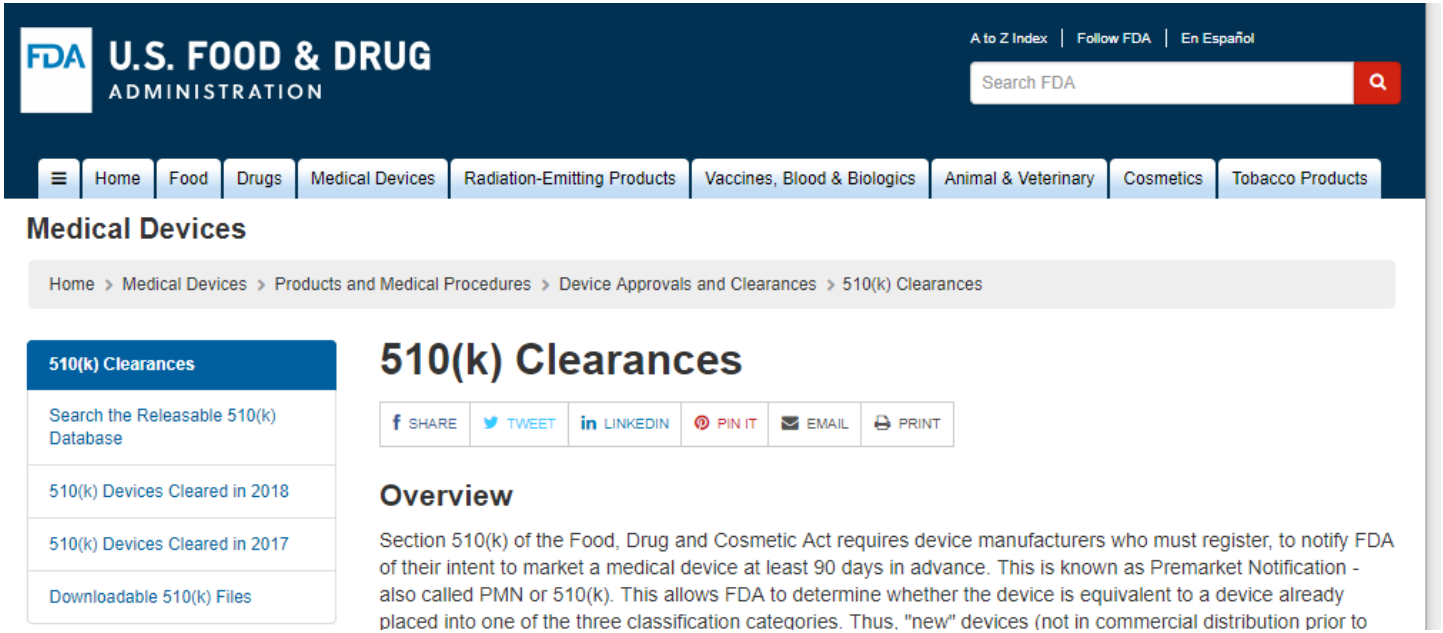
What do you think?

- Efficacy, safety, non-inferiority, superiority (phase II / III)

- PT vs RT: tumor control non-inferiority
- PT vs RT: toxicity improvement
- FLASH vs std dose rate: tumor control non-inferiority
- FLASH vs std dose rate: toxicity improvement
- 3DCRT vs IMRT: tumor control non-inferiority
- 3DCRT vs IMRT: toxicity improvement

Technology assessment

- Level 1 evidence of non-inferiority or superiority **not necessary** for market authorization for technology / technique



RT vendors aren’t that rich compared to pharma

Need for evidence

"Although most of the proton centers in the United States are profitable, the industry is littered with financial failure: **nearly a third of the existing centers lose money**, have defaulted on debt or have had to overhaul their finances."

(…)

"…**has not been shown to be more effective against** breast, prostate and other common cancers. One recent study of lung-cancer patients found no significant difference in outcomes between people receiving proton therapy and those getting a focused kind of traditional radiation, **which is much less expensive**.

(…)

"Commercial insurers are just not reimbursing" for proton therapy except for pediatric cancers or tumors near sensitive organs, substantially limiting the potential treatment pool

https://www.nytimes.com/2018/04/27/business/proton-therapy-finances.html

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Potential pitfalls

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Potential pitfalls

- HTA Authorities/payers: evidence of efficacy and cost effectiveness required before reimbursement.
- For evidence you need evidence collection, e.g. trial.
- No reimbursement, no trial.
- No trial, no evidence.
- The “Catch 22” of expensive equipment

Potential pitfalls

- Equipoise
  - Do we really doubt that A is better than B?
  - Physician
  - Patient preference
- Ethical
- Financial
  - You need the machine to test the machine (technology)
- Timelines
  - 10 years between idea and publication
  - An eternity in terms of tech development

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Example of technology assessment

Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer

Zhongxing Liao, J. Jack Lee, Ritsuko Komaki, Daniel R. Gomez, Michael S. O'Reilly, Frank V. Fossella, George R. Blumenschein Jr, John V. Heymach, Ara A. Vaporciyan, Stephen G. Swisher, Pamela K. Allen, Noah Chan Choi, Thomas F. DeLaney, Stephen M. Hahn, James D. Cox, Charles S. Lu, and Radhe Mohan

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Shameless plugin

EORTC Courses

Clinical Trial Statistics for Non Statisticians

Example of technology assessment

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Hypothesis: 10% reduction in grade 3 or more radiation pneumonitis for PSPT vs IMRT

Conclusion

PSPT did not improve dose-volume indices for lung but did for heart. No benefit was noted in RP or LF after PSPT. Improvements in both end points were observed over the course of the trial.

Example of technology assessment

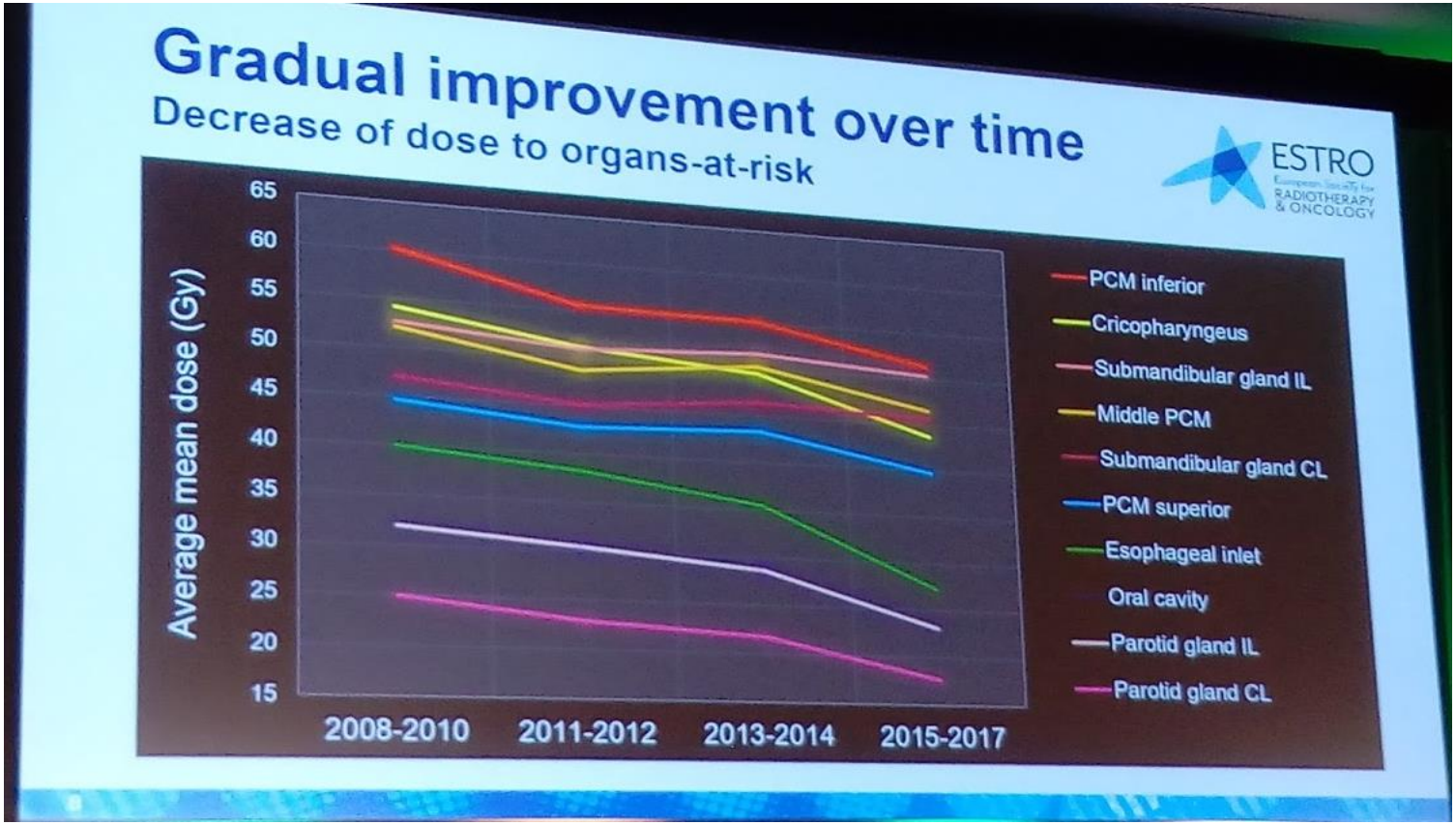
What Happens When Proton Meets Randomization: Is There a Future for Proton Therapy?

Feng-Ming (Spring) Kong, *Indiana University School of Medicine, Indianapolis, IN*

In summary, this randomized trial showed no benefit of proton therapy to reduce serious lung toxicity in the treatment of locally advanced NSCLC compared with IMRT with the technology available at that time.

The randomized trial should only include patients for whom the use of protons provides a better dosimetric plan. Such a randomized trial will identify patients with proven dosimetric superiority from proton planning to demonstrate whether such a dosimetric advantage can be translated into clinical benefit.

The learning curve



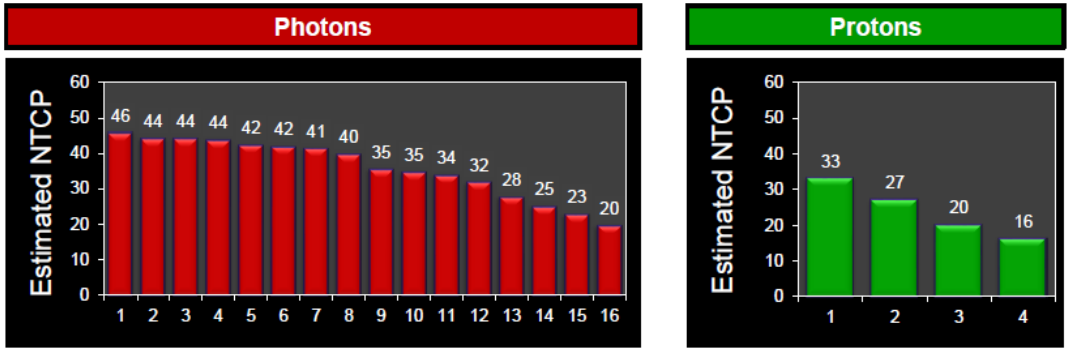
History of dose to healthy tissue given to H&N patient in a Dutch institution
Courtesy of H. Langendijk, EPTN session, ESTRO37

The learning curve

Variability between centers

Endpoint: NTCP for dysphagia grade II-IV

umcg



Courtesy: Wilco Verbakel (Dutch Platform for Head and Neck Radiotherapy)

- Planning comparison study
- Multicenter (n=16)
- One patient
- One set of targets
- One set of OAR's

Courtesy of H. Langendijk, ESTRO37

Example of technology assessment

What Happens When Proton Meets Randomization: Is There a Future for Proton Therapy?

Feng-Ming (Spring) Kong, *Indiana University School of Medicine, Indianapolis, IN*

- No significant change in Mean Lung Dose in PT vs RT
- RT is in its prime, PT was new to the team
  - Pts later in the trial had superior PT
  - All RP events early in PT arm, evenly spread for IMRT arm
- Estimated Radiobiological Effectiveness might be off
- Imbalance in margins definition and adaptive planning
- Denial for IMRT (by patients) and PSPT reimbursement (by insurance)

Coping Strategies

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INDEPENTENT R/PTQA

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PATIENT ENGAGEMENT

Parenthesis: patient engagement

RadComp™
PATIENT POWERED
A study at the heart of breast cancer treatment

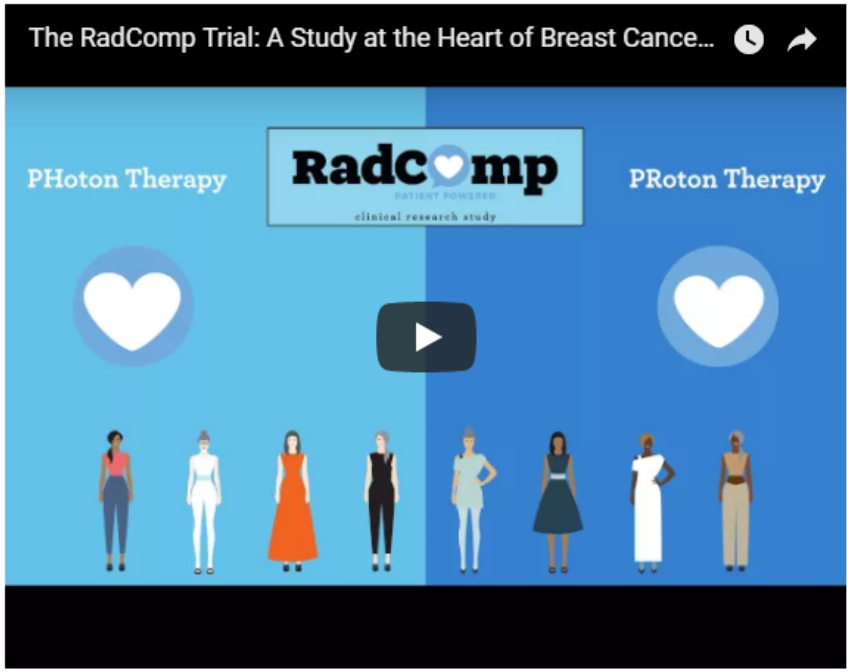
RadComp Patients
Personnel

HOME | STUDY TEAM | NEWS | FIND A SITE

THE RADCOMP STUDY

The RadComp Study, short for Radiotherapy Comparative Effectiveness, is a nationwide clinical study comparing two FDA approved radiation therapies for the treatment of breast cancer, PHoton Therapy vs. PRoton Therapy. With this study, we hope to better understand the best available technologies for breast cancer to help patients live a longer, healthier life.

Check out this short video for an overview of the study and how you can participate:



RadComp is "Patient Powered"

RadComp was designed with help from breast cancer patients. Patients told us they were most concerned about heart problems after therapy and how radiation might affect their quality of life. Thus, this study seeks to learn which type of radiation, PHoton Therapy vs. PRoton Therapy, will help breast cancer patients avoid heart problems, live longer, and have a better quality of life.

Coping Strategies

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Patient enrichment and model based approach

COMMENT

Professor Dirk De Ruysscher,
radiation oncologist, Maastricht University Medical Centre, Department of Radiation Oncology (Maastro clinic), The Netherlands

Proton therapy (PT) has been around for decades and except for some rare tumours, its benefit remains uncertain and is the subject of many controversies and vigorous pro- and contra debates in the literature and at scientific meetings. The reason for this disagreement is that although the irradiated low-dose volume is generally lower with PT than with photons, no clear clinical benefit for PT has been reported for the majority of patient groups [1,2]. A major critique to the PT community is the lack of randomised studies comparing PT to photons. This is often countered by the argument that a reduction of the radiation dose to organs at risk should be beneficial.

The authors of this first randomised trial should therefore be applauded [3]. Even though the outcome for patients was similar for PT and photons, this trial is educative in many respects. As pointed out in an excellent accompanying editorial by Dr Kong [4], although the low-dose areas in the lungs (V5-V10) were reduced by PT, the higher dose regions (V20 and higher) were similar in both arms and the V50 + was even bigger with PT than with photons. The mean lung dose was the same. Even in these highly experienced centres, there was a learning curve, with more recent patients showing an improved outcome, both for PT and for photons. The Bayesian study design contributed to an imbalance between both arms. It can also be questioned if the biological effect of protons was modelled adequately.

In a very interesting abstract presented at the ESTRO 36 congress, Deist and colleagues showed in an exploratory analysis of the same trial that the high dose regions in the lungs have a more pronounced effect on the pulmonary toxicity than the low-dose volumes, both in PT and in photon therapy [5]. This underscores the importance to develop adequate models allowing to select patients for PT, which is the basis for the "model-based" strategy in The Netherlands [6].

In my opinion, there is no argument to randomise all patients between PT and photons without a selection model. In the study design of Liao et al, the DVH parameters of the lungs (co-primary endpoint was radiation pneumonitis) in both arms came pretty close to each other, with a similar incidence of radiation pneumonitis as a result. In future studies, we should first optimise the prediction models for the primary endpoint of the study. Thereafter, the models should be validated prospectively. For some patients, there will be a clear indication for PT whereas for most photons will remain the first choice treatment. For a third, intermediate group, clinical equipoise will remain, and these may be suited for randomised trials between PT and photons.

This strategy may work as well for the objective assessment of other technological innovations in radiation oncology, leading to more solid evidence in our specialty.

DIRK DE RUYSSCHER

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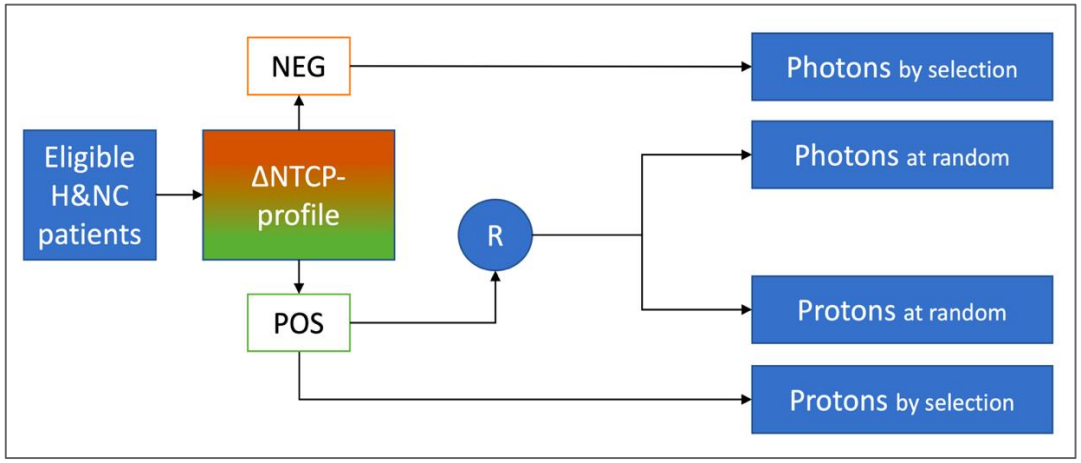
What EORTC is doing

State of Science Meeting

1



2

Multicenter randomised phase II study evaluating the feasibility and efficacy of the combination neoadjuvant FOLFIRINOX followed by SBRT with and without nanoparticles in borderline resectable and locally advanced pancreatic cancer

Talking to companies

- Table with IBA, VARIAN, COCIR

Alternatives to trials?

- “(…) the best available evidence is required. This distinction may be relevant where RCTs may not be possible, ethical or generalizable to routine practice, or when observational evidence may be compelling.”
- “Improving cure rates was considered likely to prove cost effective, whereas showing cost effectiveness based on a reduction in toxicity is much more difficult.”

MCR NCRI CTRad Workshop on methodological challenges and opportunities in radiotherapy research, 2010

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Alternatives to trials?

GUIDANCE DOCUMENT

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

AUGUST 2017

Download the Final Guidance Document

Final

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Real World Evidence

- National/international registries
- National/international platforms

Wait and look for:

- Emerging patterns of care
- Emerging patterns of toxicity
- Emerging patterns of…

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Real World Evidence

- National/international registries
- National/international platforms

Wait and look for:

- Emerging patterns of care
- Emerging patterns of toxicity
- Emerging patterns of…
- ! exploratory !
- ! hypothesis generation !

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No, seriously

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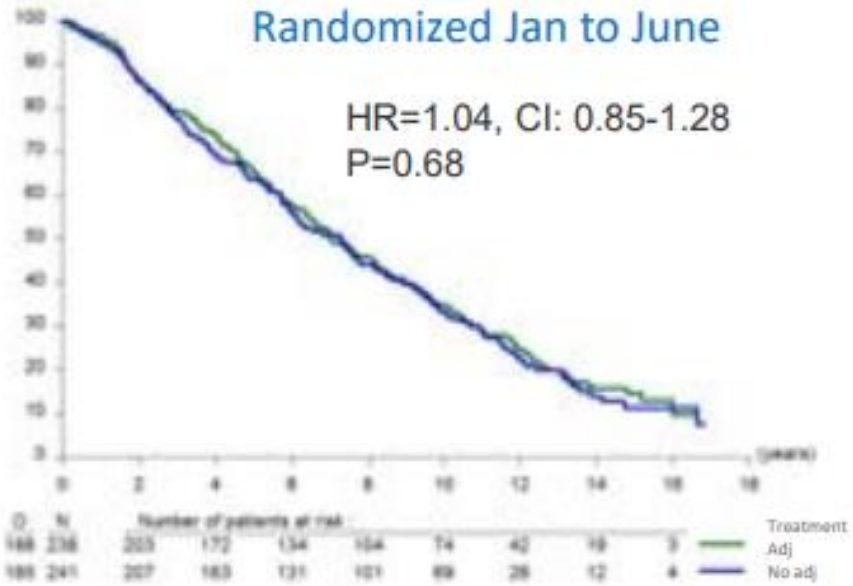
Clinical Trial Statistics for Non Statisticians

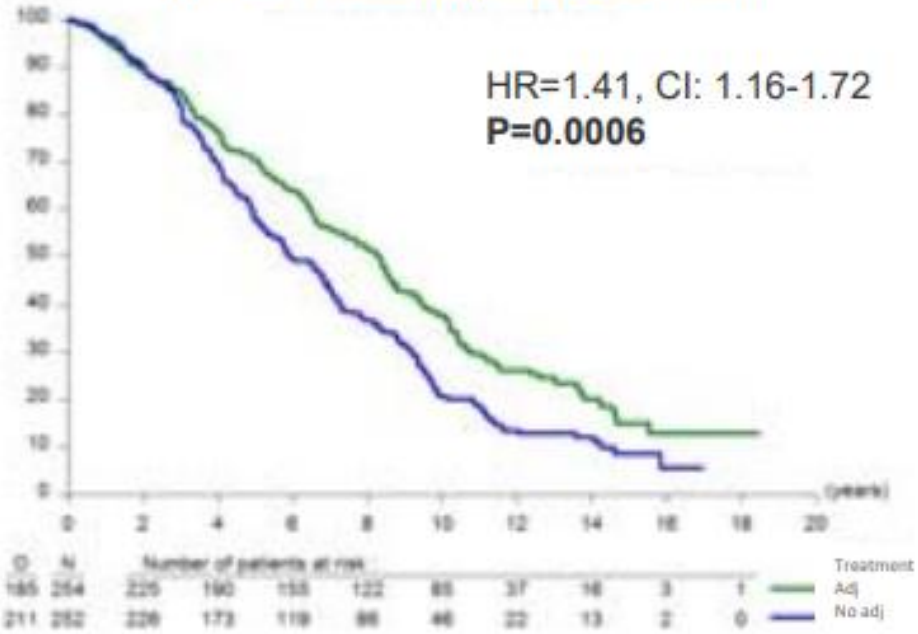
What's going on here? Seasonal effect?

Overall survival
Randomized Jan to June



Interaction P=0.03

Overall survival
Randomized July to December



Courtesy of L. Collette

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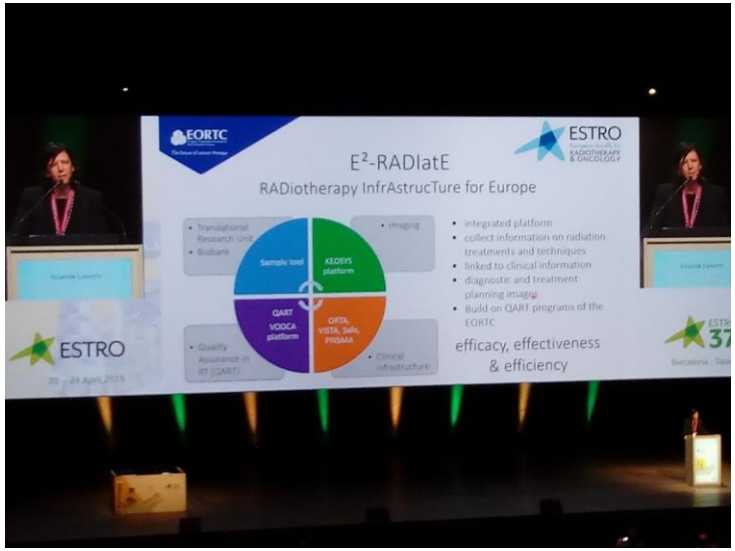
E²RADiatE

EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe E²RADIatE

prospective data registration platform



E²-RADIatE Steering Committee

E²-RADIatE

Coordinating Committee

OligoCare

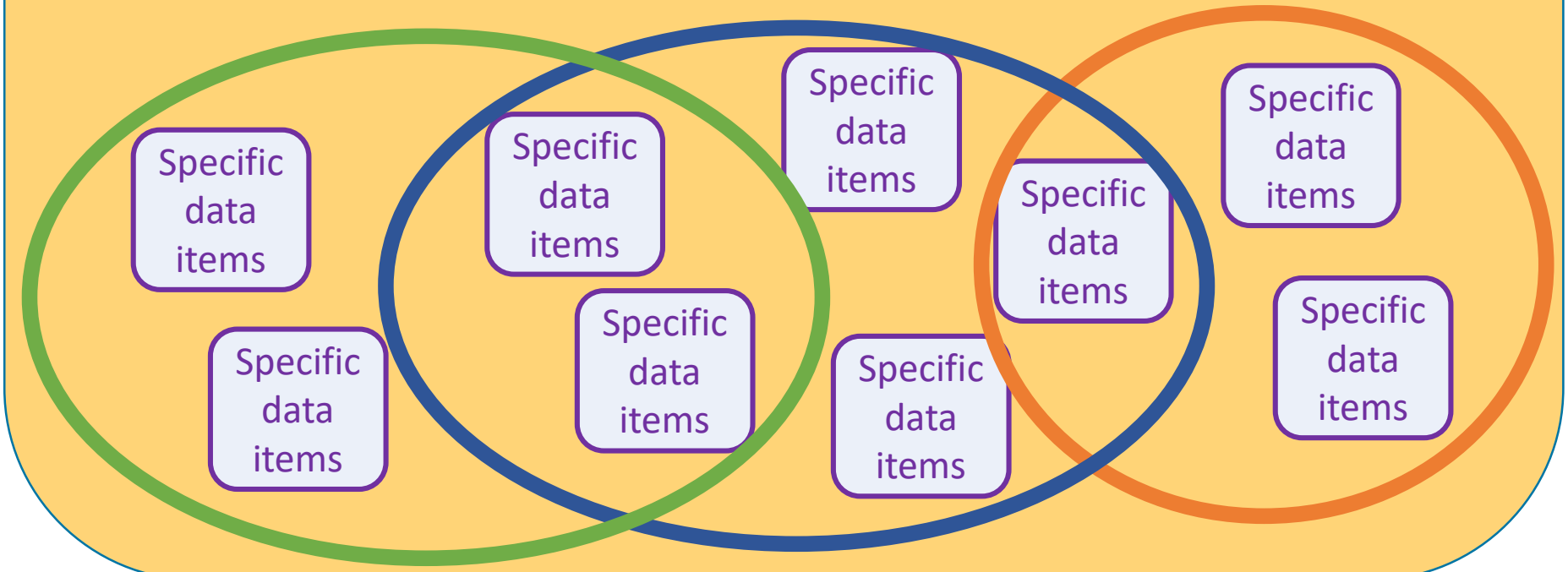
Coordinating Committee

ParticleCare

Coordinating Committee

Cohort X

Core E²-RADIatE data items



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E²RADiatE

EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe E²RADIatE

prospective data registration platform

- STREAMLINE site activation to studies
- Capture a baseline limited dataset
- Research projects can plug-in and extend
- Longitudinal tracking
- Hypothesis generating platform

E²RADiatE

EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe E²RADIatE

prospective data registration platform

- OligoCare (Piet Ost, Matthias Guckenberger)
  - First site open 06/2019
- ParticleCare (Hans Langendijk, Cai Grau, EPTN)
  - First site will open 09/2019

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In summary

- RCT-level evidence still the gold standard
- RT/PT assessment trials
  - Quality assurance
  - Patient involvement
  - Coverage with evidence generation (HTA Authorities)
  - Patient enrichment via model based approach
  - Non-standard methodology (Bayesian, adaptive, etc.)
  - Go international
- Real World Evidence:
  - Observe emerging patterns
  - Generate hypothesis


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