Cancer and Non-cancer Risks from Emerging Radiotherapy Techniques

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Outline

- What are emerging radiotherapy techniques?
- What's the goal and the questions?
- Trends and patterns of use
- Studies of potential cancer and non-cancer risks
  - Indirect - modeling
  - Direct – patient follow-up

Take Home Message

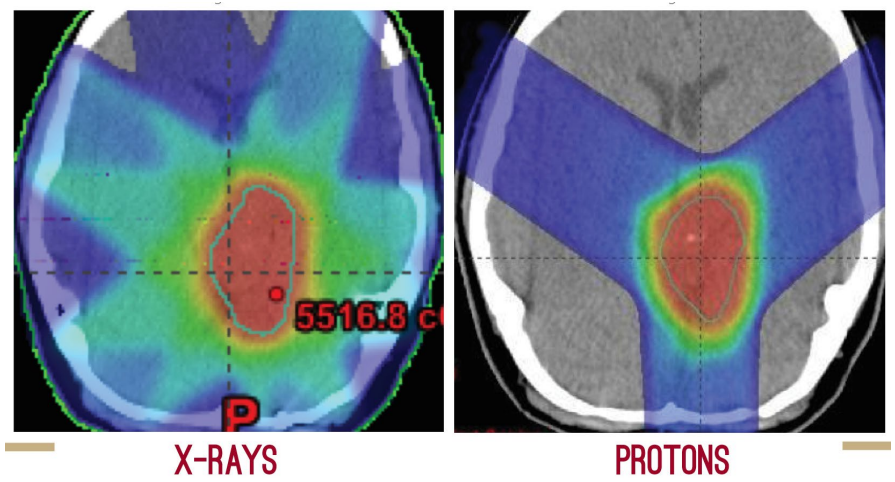
- **Will emerging radiotherapy techniques decrease late effects?**
  - **They should do, but we don’t know by how much yet**

Emerging Radiotherapy Techniques?

- **IMRT/VMAT, protons, carbon ions….flash RT, microbeam RT**

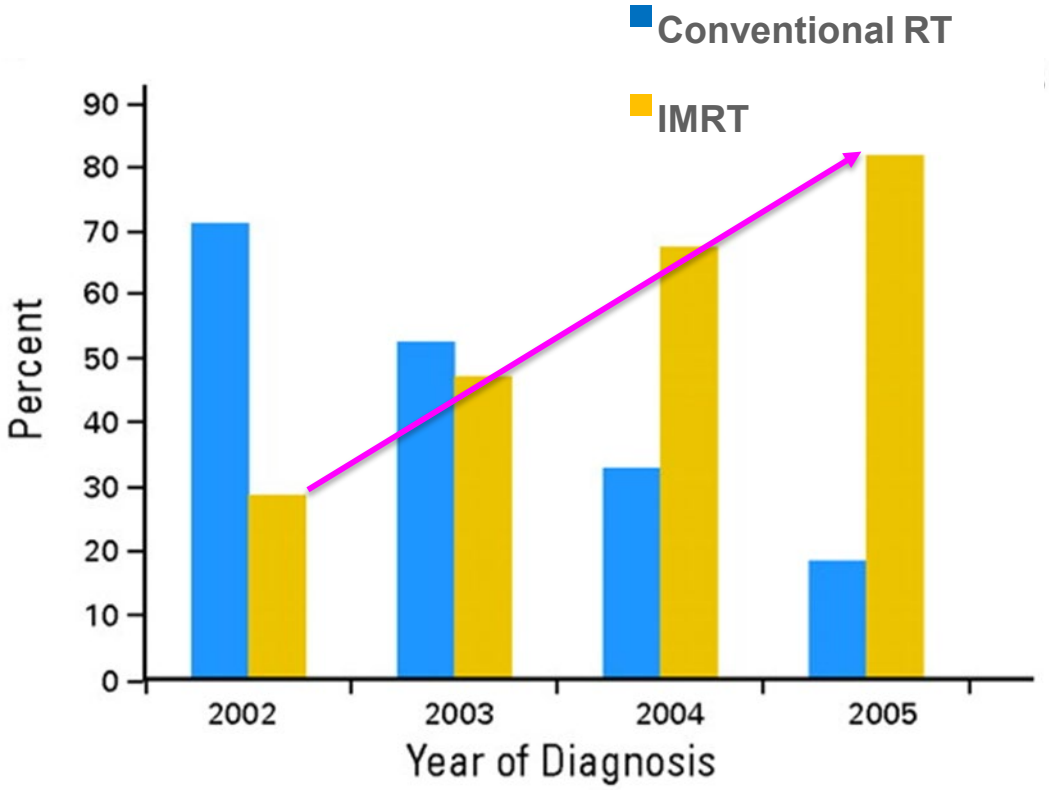
Goal of Emerging Radiotherapy Techniques?

- Reduce high-dose exposure to normal tissues
- Reduce acute toxicities & late effects in/near field
- But….at the expense of increased scatter (low) dose?



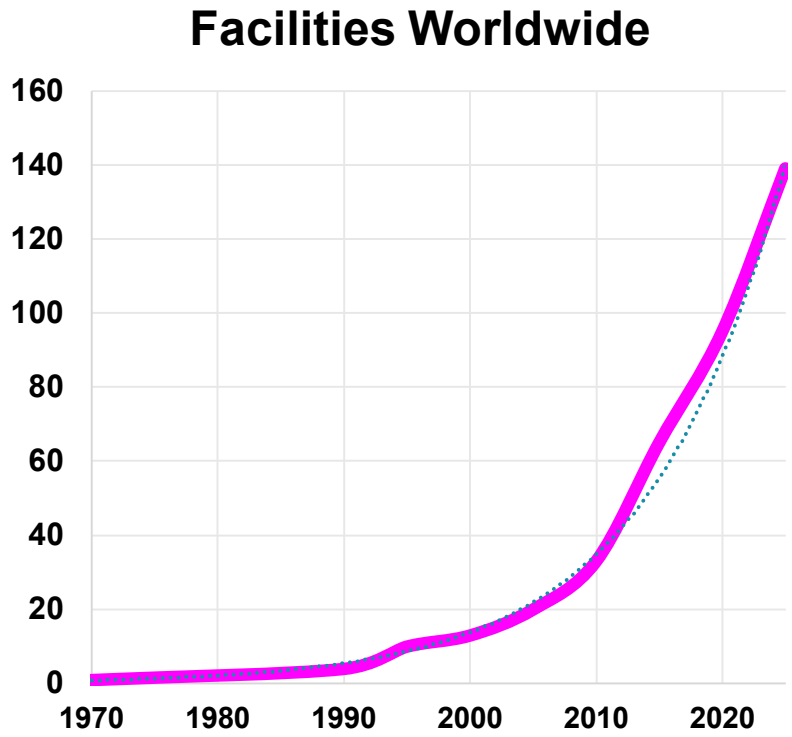
Patterns of Use

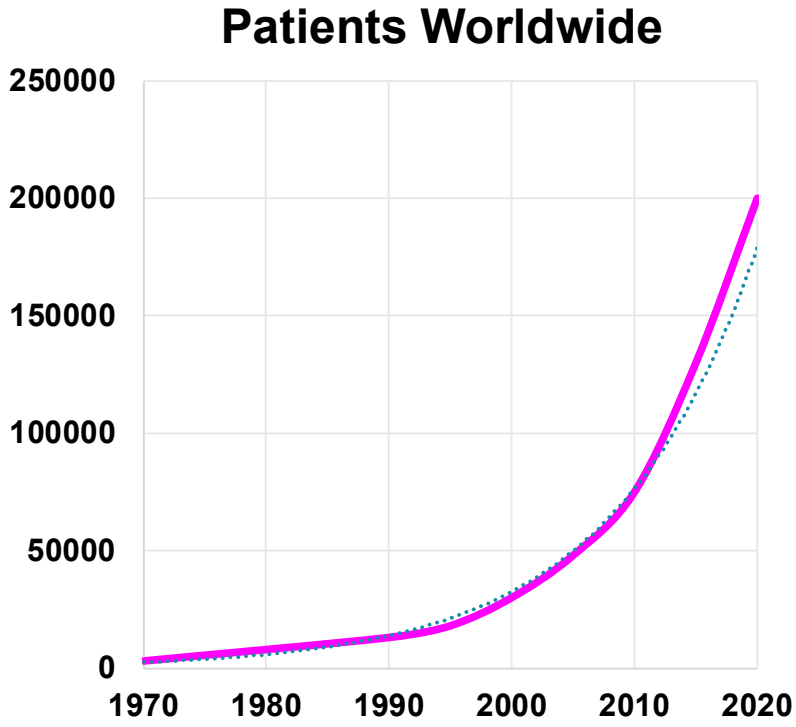
Rapid Adoption of IMRT:
eg Prostate cancer radiotherapy (Medicare USA)



Nguyen et al (JCO

Exponential Expansion in Proton Therapy





Source: PTCOG website

Who is Being Treated with Protons?

International Pediatric Proton Therapy Survey: 2016

- 39 of 54 centers replied (72%) and 20 of 23 US centers
- Estimated 2000-2500 pediatric patients treated in 2016
  - Doubled since 2012 survey
- 24% of patients <age 5 and 50% <age 10
- 33% treated with passive scattering
  - Neutron scatter dose RBE 20?

Journy, Indelicato,…Kleinerman, Berrington (Radiotherapy & Oncology, 2019)

Pediatric RT Patients Treated with Protons in USA: 2016

	% pediatric RT patients
Rhabdomyosarcoma	54%
Medulloblastoma	50%
Ependymoma	68%
Ewing sarcoma	53%
Hodgkin lymphoma	18%
All pediatric cancers	20%

Journy, Indelicato,…Kleinerman, Berrington (Radiotherapy & Oncology, 2019)

USA Adult Proton Surveys

	2012	2016	% 2016 RT patients*
Prostate	2300	?	4%
CNS	600	1200	8%
Head & neck	300	900	3%
Breast	100	700	0.5%
Total	5400	9200	nk

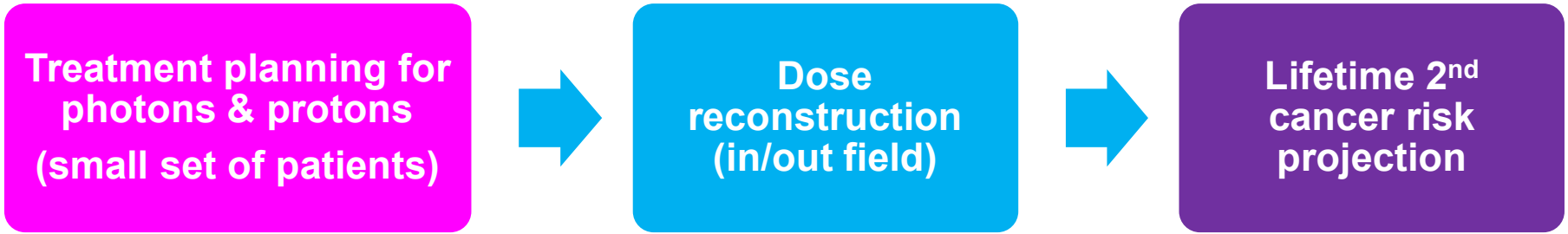
National Association for Proton Therapy (NAPT)

*Back of envelope!

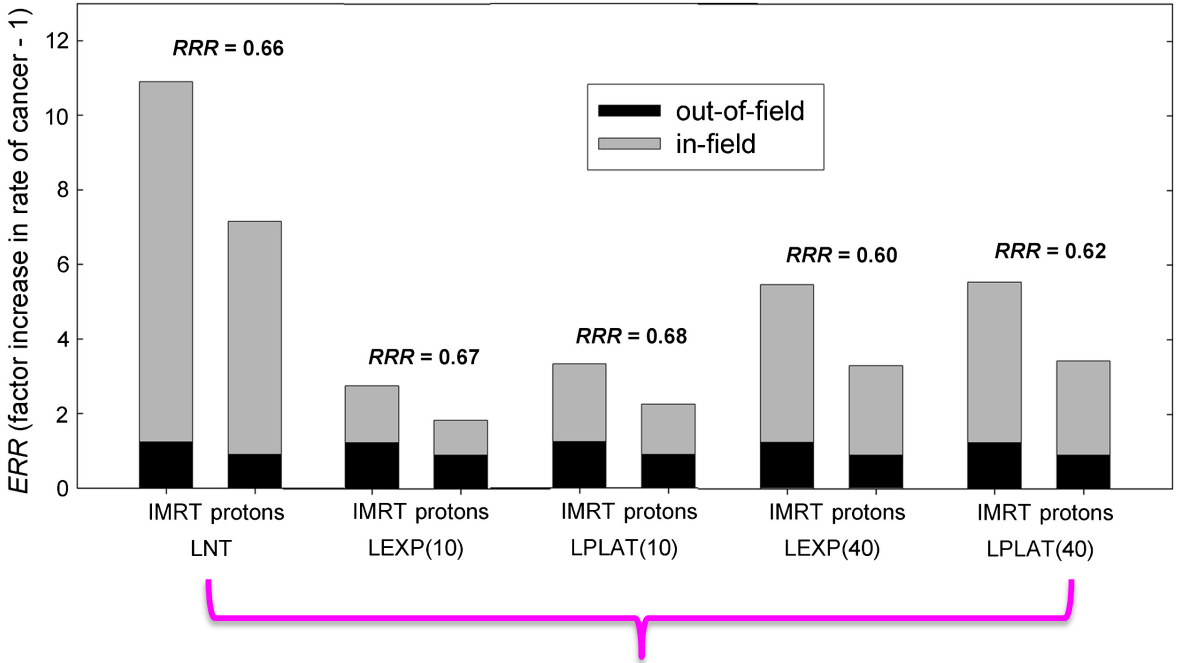
Epidemiological Data

“By definition we cannot observe the late effects of current treatments.”

Indirect Approach: Modeling Studies



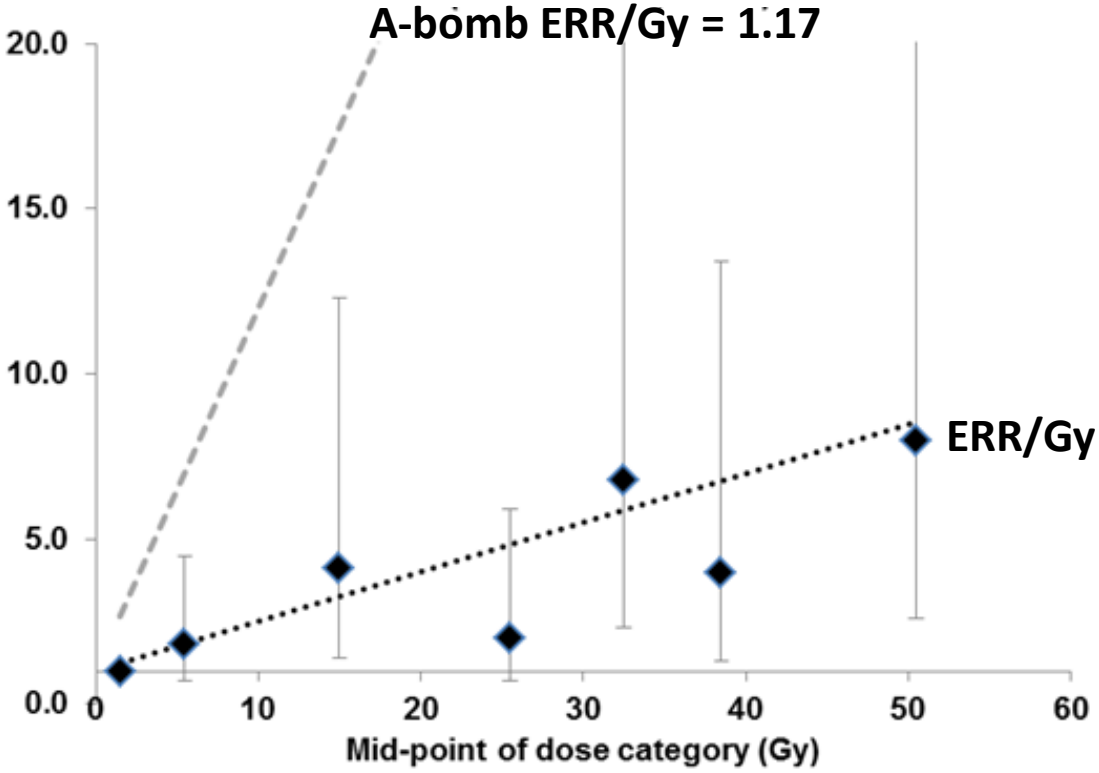
Example of Indirect Approach:
Risk Projection for Prostate Cancer (n=3) using A-bomb LSS



Dose-response assumptions to extrapolate A-bomb to high dose fractionated exposure

Fontenot et al (IJROBP 2009)

A-bomb vs Radiotherapy Dose-response Comparison
Example: Breast Cancer after Hodgkin Lymphoma



Ratio = 7.8

Berrington de Gonzalez et al (IJROBP, 2013)

Ratio of ERR/Gy for A-bomb vs Radiotherapy

Organ	RT studies	Ratio
Breast	3	5-16
Brain	5	0.2-16
Esophagus	1	8
Lung	2	6-10
Stomach	1	0.5
Thyroid (non-linear)	3	0.8-2

Ratio assumed constant across 2nd cancer sites in modeling studies

Berrington de Gonzalez et al (IJROBP, 2013)

Modeling Studies Assumptions

- Dose planning typical for wide-variety of real patients
- Transport of A-bomb risk models to high-dose fractionated RT
- Dose-volume effects
- RBE for neutrons and protons

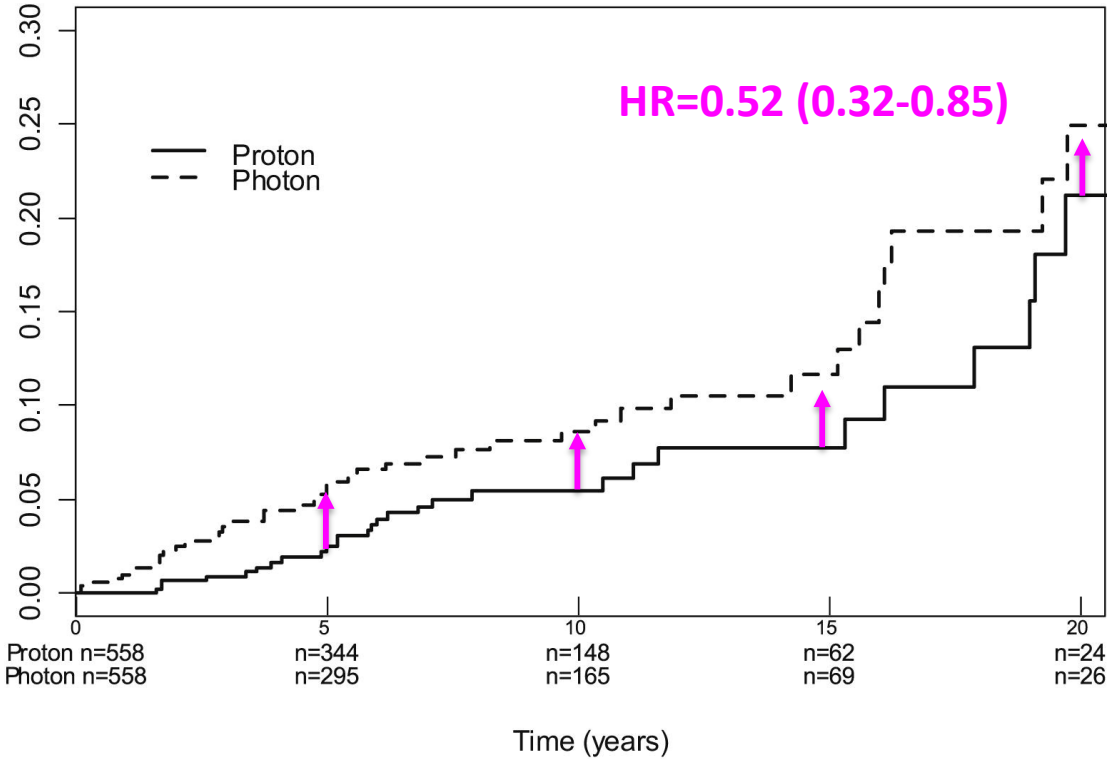
Study Designs for 2nd Cancers after Radiotherapy

Design	Advantages	Disadvantages
Single institutions	Detailed treatment	Small N Completeness of follow-up?
Cancer registries	Large N Long-term follow-up Highly complete	Limited treatment data Potential confounding
Dose-response case-control studies	Detailed treatment Quantify risk per unit dose	Expensive & time consuming

Single Institution Example: Pediatric proton therapy

MGH Retrospective Study of Proton Patients (n=588) & SEER registries external matched comparison

% 2nd cancer



Chung et al IJROBP (2012)

Registry Example: IMRT for Prostate cancer

IMRT vs 3D-CRT for Prostate Cancer

USA SEER-Medicare

- 1st cancer = prostate
- Age 65-84 years

IMRT vs 3D-CRT

- Claims data 2002-2009
- 39k RT patients

Follow-up to 2011

- 2nd cancers
- Death/end of study

Journy…Berrington (JAMA Oncology, 2016)

PPCR

Pediatric Proton Consortium Registry

- The ***Pediatric Proton Consortium Registry*** is a collaborative effort between 20+ proton centers across the US established to expedite proton outcomes research

13 active sites open to accrual since October 2012:

UFHealth Proton Therapy Institute

MGH 1811 Massachusetts General Hospital

Mayo Clinic

University of Pennsylvania Abramson Cancer Center

The University of Texas MD Anderson Cancer Center Proton Therapy

Northwestern Medicine Chicago Proton Center

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

ProCure Proton Therapy Center

Washington University in St. Louis

Maryland Proton Treatment Center Affiliated with University of Maryland Marlene and Stewart Greenebaum Cancer Center

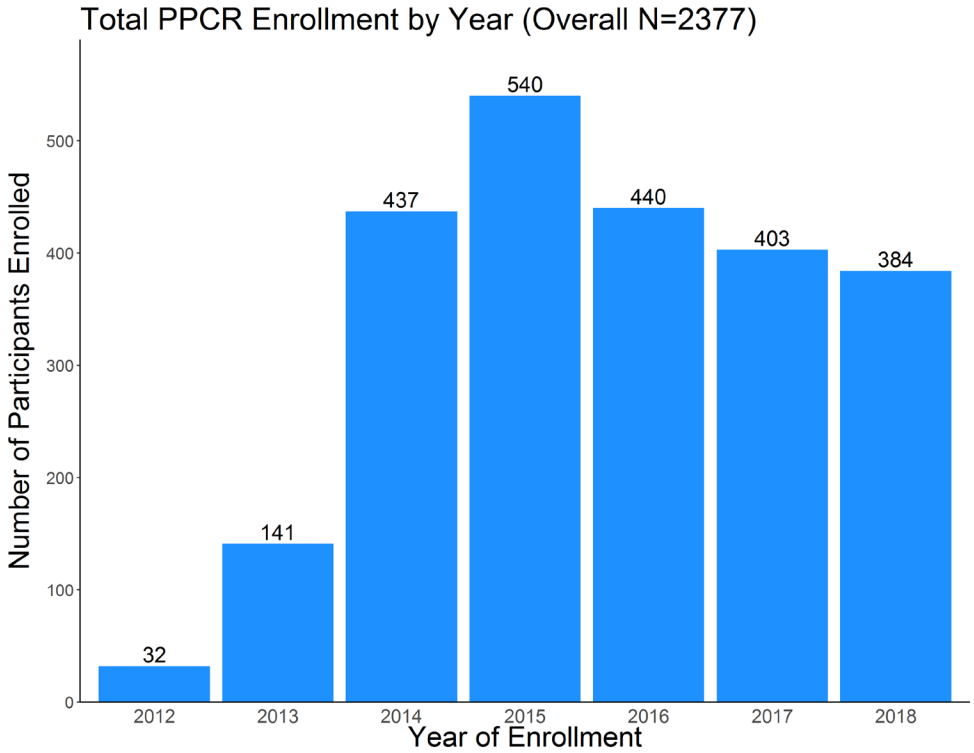
Texas Center for Proton Therapy

Cincinnati Children's changing the outcome together

UC Health

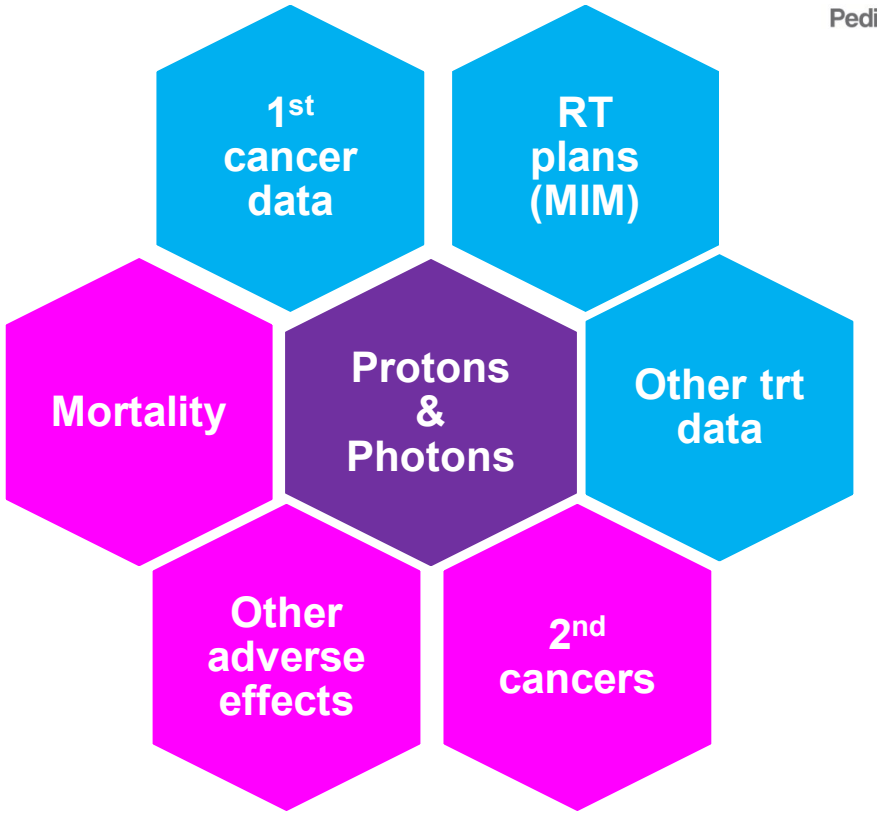
PPCR

Pediatric Proton Consortium Registry



US Pediatric Proton Therapy Cohort

PPCR
Pediatric Proton Consortium Registry



Randomized Trial Example: Breast cancer proton therapy

Radcomp

- 1300 Breast cancer patients randomized to protons vs photons
  - 3yr recruitment = 640 women
  - 22 US proton therapy centers

- Primary aims:
  - Reduction in major cardiovascular events
  - Non-inferiority for recurrence

Bekelman et al (BMJ Open, in press)

Summary

- Emerging radiotherapy techniques aim to reduce short & long-term toxicities
- Expanding rapidly, but….

- Late effects of emerging technologies still uncertain
  - Risk projections models – require assumptions
  - Well-designed comparative studies needed

Quiz questions

Question 1

What's the main aim of emerging radiotherapy techniques?

a) Reduce high-dose exposures to normal tissues

b) Reduce low-dose (scatter) exposures to normal tissues

Question 2

Risk modeling studies have established that proton therapy has fewer side-effects than photon therapy?

True or False?

Question 3

What's the main limitation of registry based studies of late-effects?

a) Small sample size

b) Limited treatment data

c) Long-term follow-up

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