Automated and Clinically Optimal Treatment Planning for Cancer Radiotherapy

Edelman Award 2021

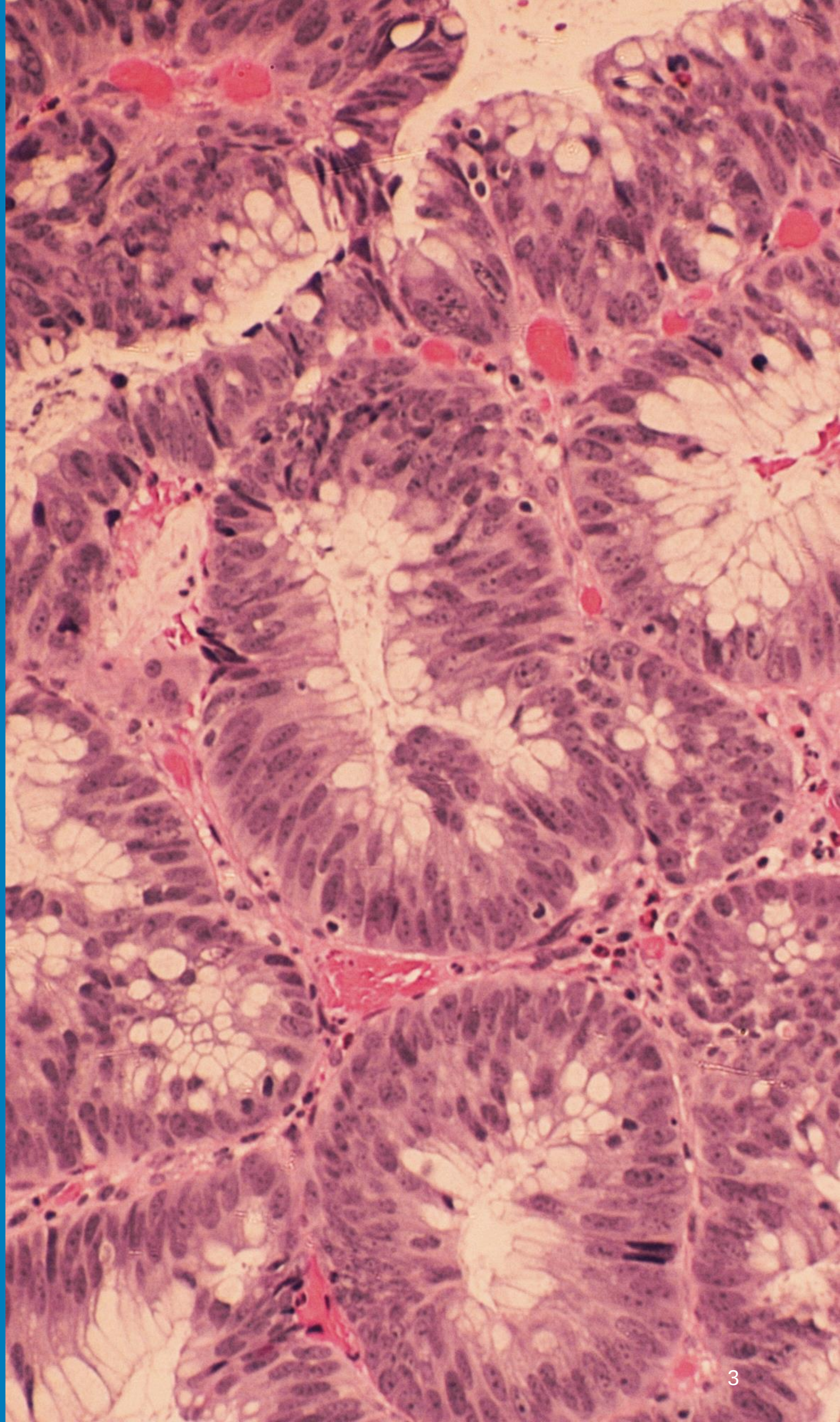
Memorial Sloan Kettering Cancer Center

Outline

- **Radiotherapy Cancer Treatment (Joseph Deasy, PhD)**
- Mathematical Modeling (Masoud Zarepisheh, PhD)
- Clinical Implementation (Linda Hong, PhD)
- Clinical Impact (Rene Brito, BS, Alex Kowalski, BS, Ying Zhou, MS, Niral Shah, MS)
- Patient Impact (Josh Yamada, MD)
- Hospital Impact (Lisa DeAngelis, MD)

The Healthcare Challenge of Cancer

- Uncontrolled growth and dissemination of abnormal cells
- Second leading cause of death after heart disease in the U.S. (2019)
- ~ 18 million new cases worldwide each year
- ~ 10 million people died from cancer (2020)
- > 1 trillion US $ (global economic cost of cancer, 2014)
- ~ 38% of men and women in the U.S. will be diagnosed with cancer at some point in their life (NCI)



Memorial Sloan Kettering Cancer Center (MSK)

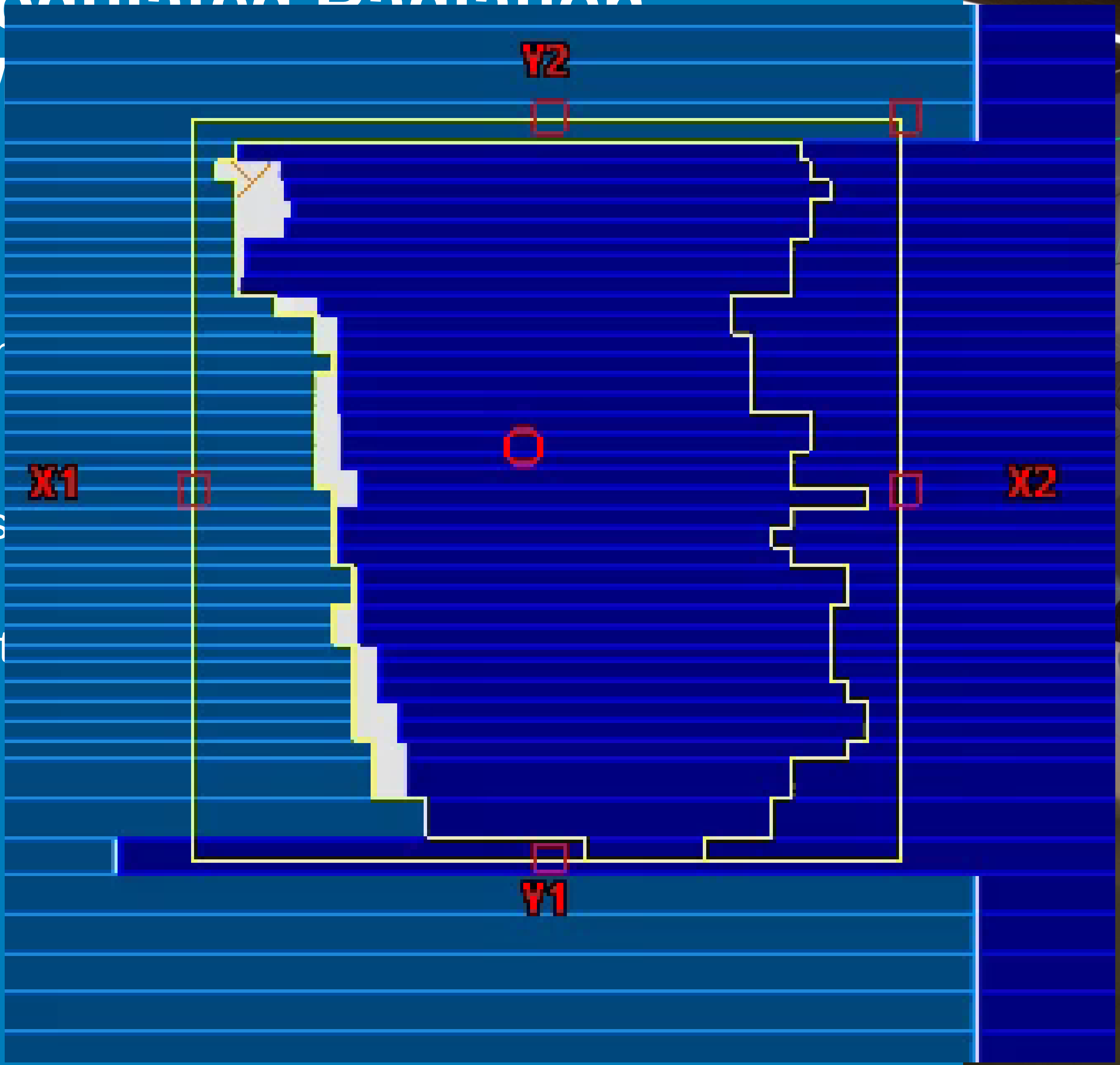
- World’s largest and oldest private cancer center
- Three missions:
  - Training (> 3,000 medical students, postdoctoral researchers, …)
  - Patient care (> 25,000 patients each year)
  - Research and development (> 120 research laboratories)
- Ranked among the top two cancer hospitals in the U.S. for more than 30 years (U.S. News)

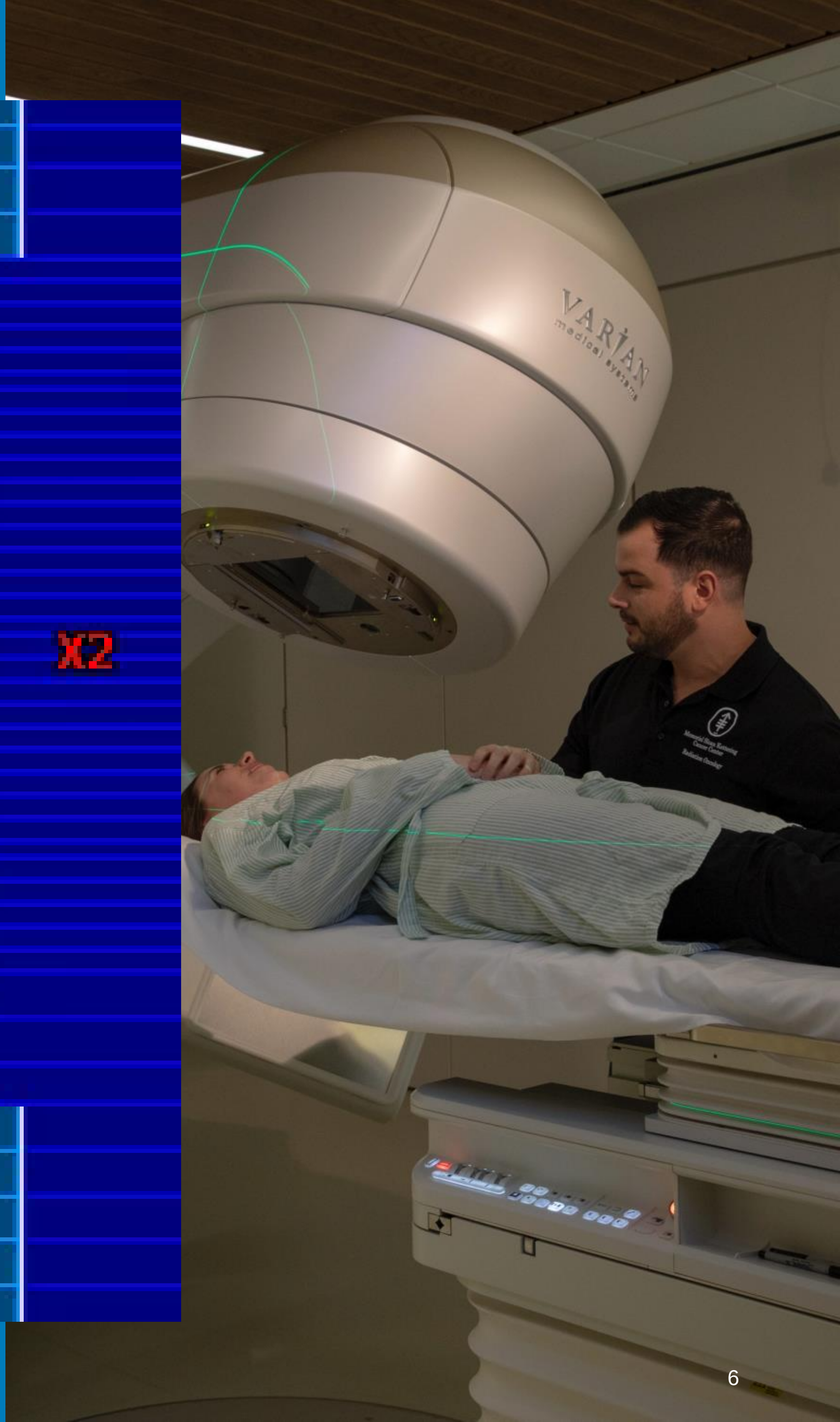
Radiotherapy: Radiation to Fight Cancer

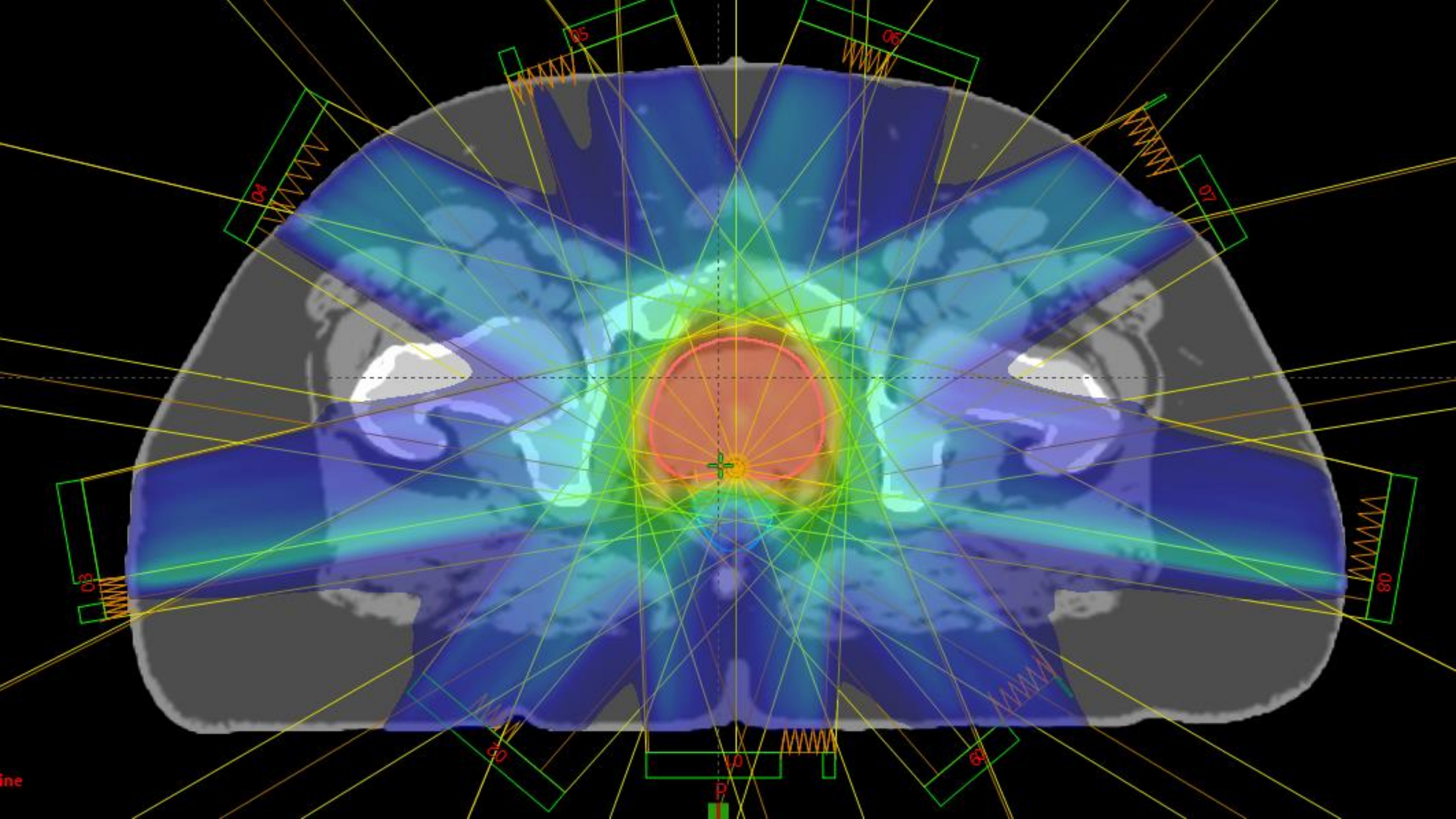
- Radiotherapy is used to treat about half of all cancer patients
- Used alone or in combination with surgery/chemotherapy
- Usually delivered in multiple treatment fractions
- Radiotherapy uses directed radiation beams to:
  - Sterilize cancer cells
  - Shrink tumors before surgery
  - Sterilize any remaining cancer cells after surgery
  - Relieve pain in palliative cases by shrinking tumors

Intensity Modulated Radiation Therapy (IM

- Electrons collide
- A multi-leaf collim rotating gantry
- The MLC shapes
- The MLC leaf pat







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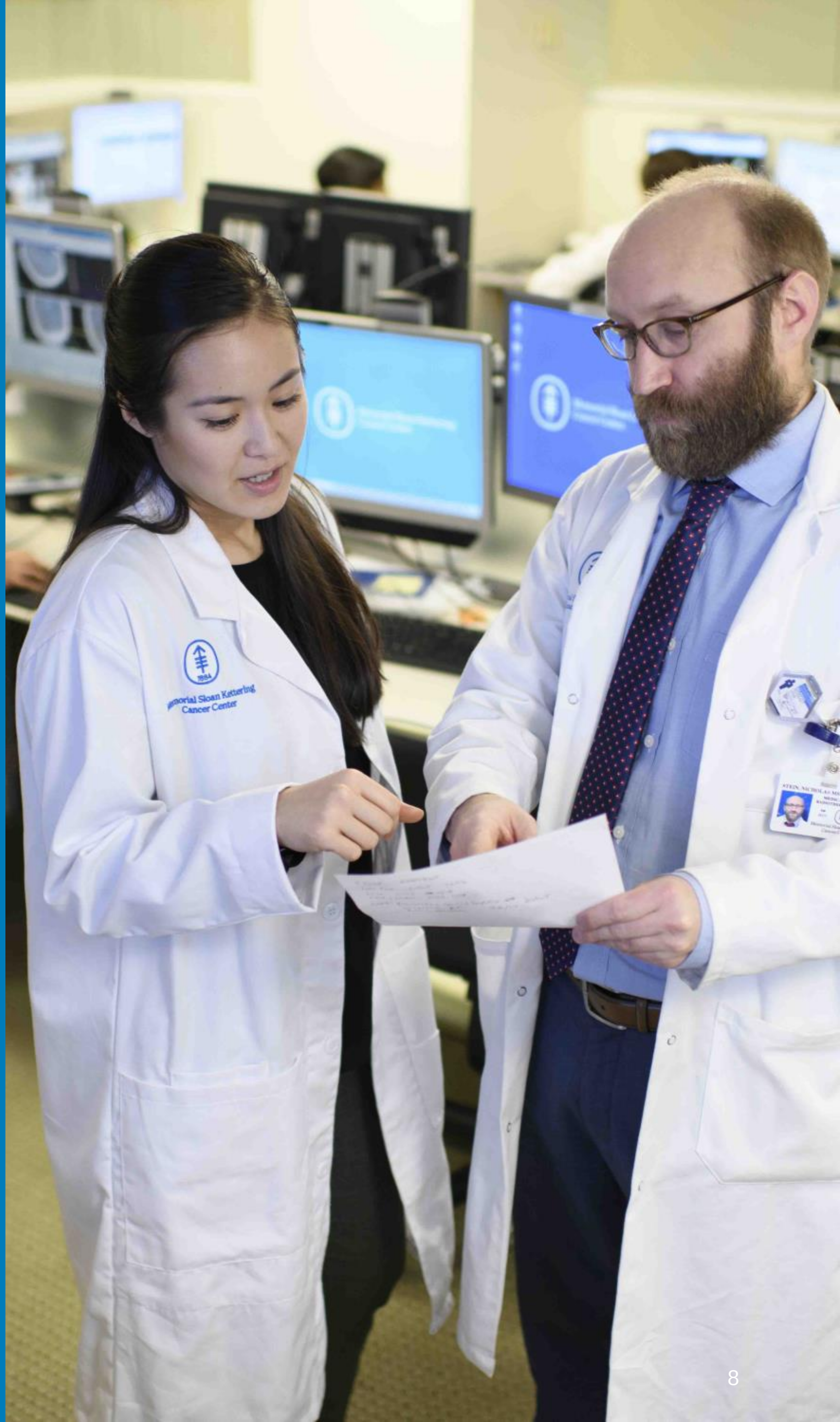
The Problem: Personalized Treatment Planning is Difficult

- Each patient is unique and needs customized treatment

- Planning performed by a medical professional (dosimetrist) and reviewed by a physician

- Current systems typically require extensive iterative hand-tuning of the optimization parameters *to control tradeoffs*

- Drawbacks: labor intensive, time consuming, variable quality



Our Solution:
ECHO
(Expedited Constrained Hierarchical Optimization)

ECHO Solves the Personalized Planning Problem Using Operations Research Tools

- ECHO planning is fast, inexpensive, high-quality, and unbiased

- Fast means:
  - Reduced time needed for planning and plan reviews
  - Shorter time to treatment for the patient
  - Avoiding unnecessary surgery for some patients

- Inexpensive means:
  - Reduced personnel resources needed for planning

- High-quality means:
  - Optimal protection of normal structures with highly effective target doses
  - Reduced risk of radiation-induced side-effects

- Unbiased means:
  - Less variability in treatment quality -- not dependent on previous plans

ECHO is a Platform for Innovation

For adapting treatments in response to changes such as tumor shrinkage

For correcting poor dosimetry in case of setup deviations

For incorporating outcome prediction models such as tumor response or injury risk

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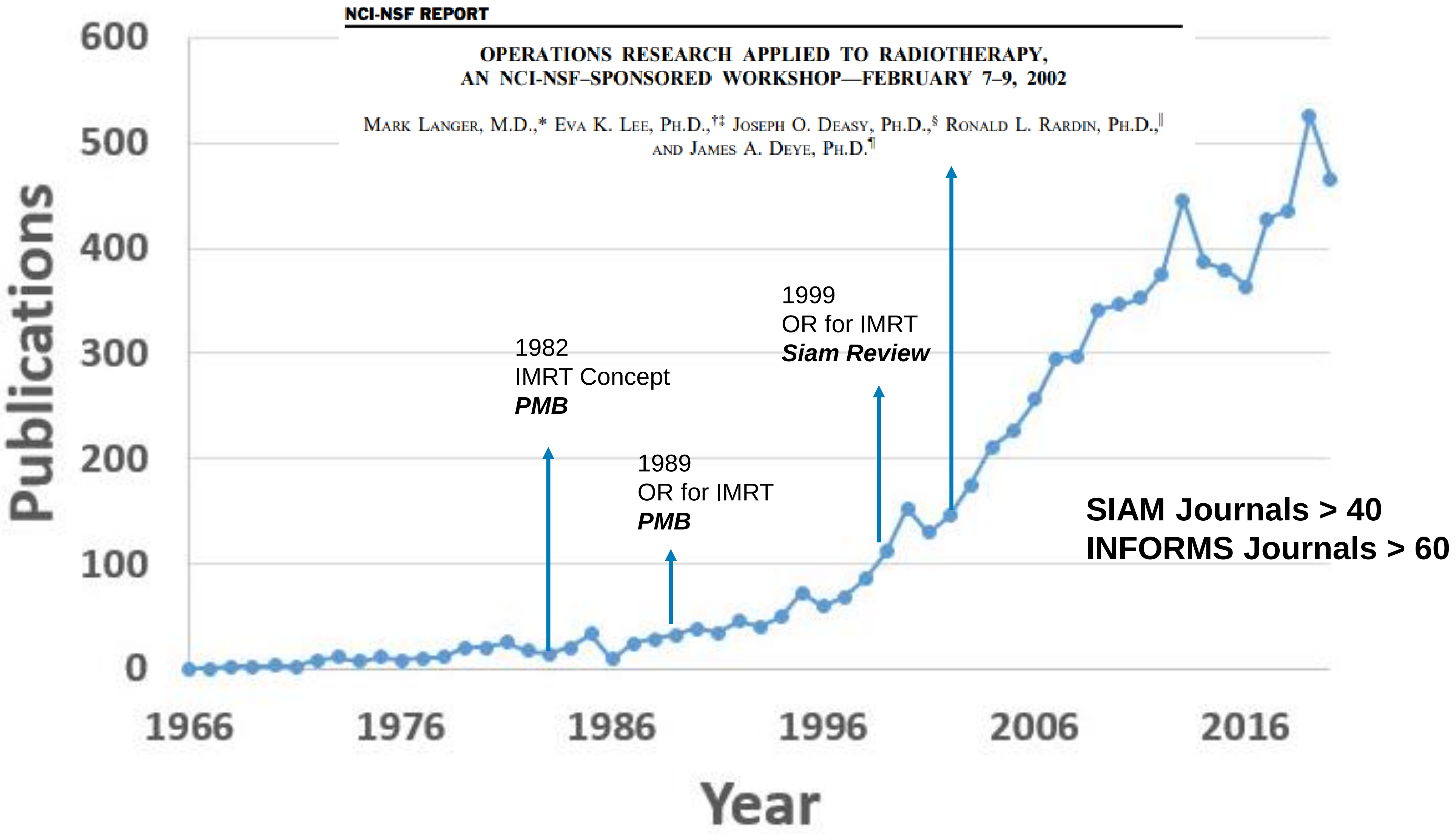
Operations Research (OR) in Radiation Therapy



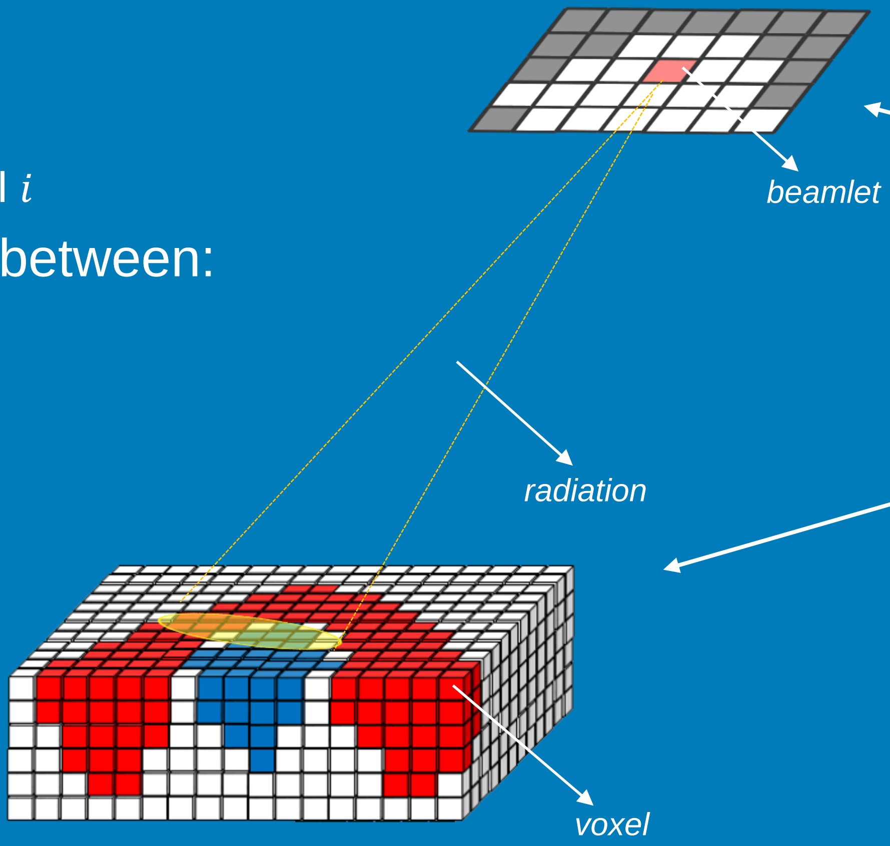
Mathematical Modeling

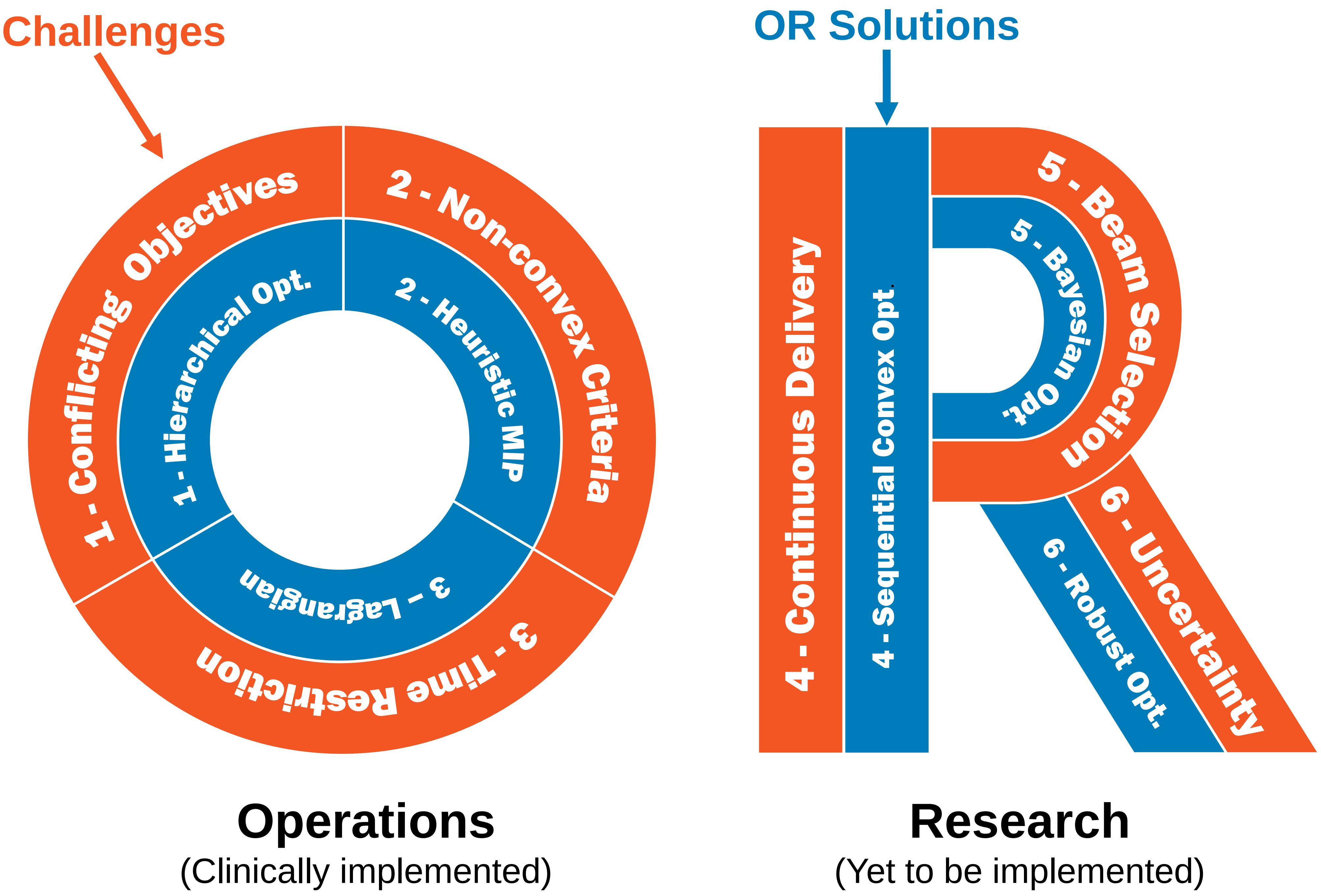
- Discretization and sampling
    - Beam into beamlets
    - Patient's body into voxels
    - A_{ji} : dose delivered from beamlet j to voxel i
- Multi-criteria Optimization. Trade-offs between:
    - Tumor irradiation
    - Nearby tissues sparing

$$d = Ax$$

x: Beamlet intensities
A: Linear map
d: Delivered radiation

$$Min\left(f_1(A^1x), \dots, f_s(A^sx), h(x)\right)$$
$$x \geq 0$$

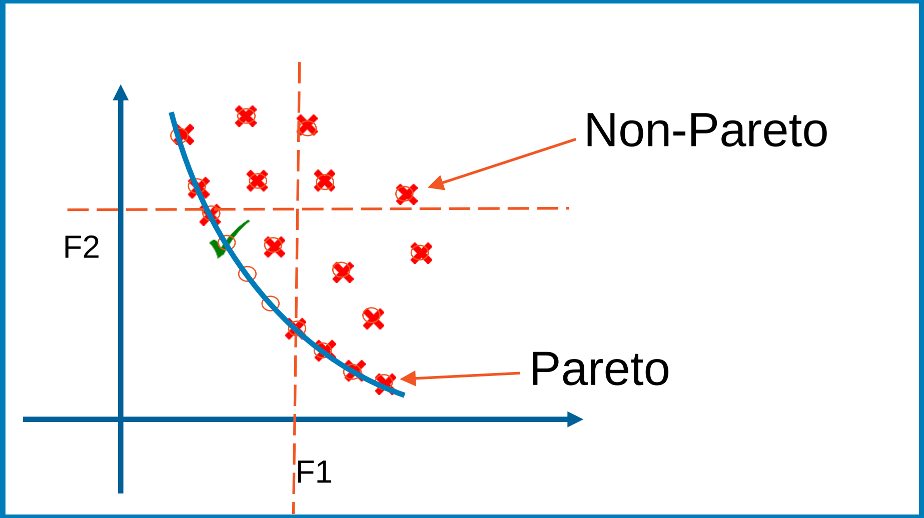


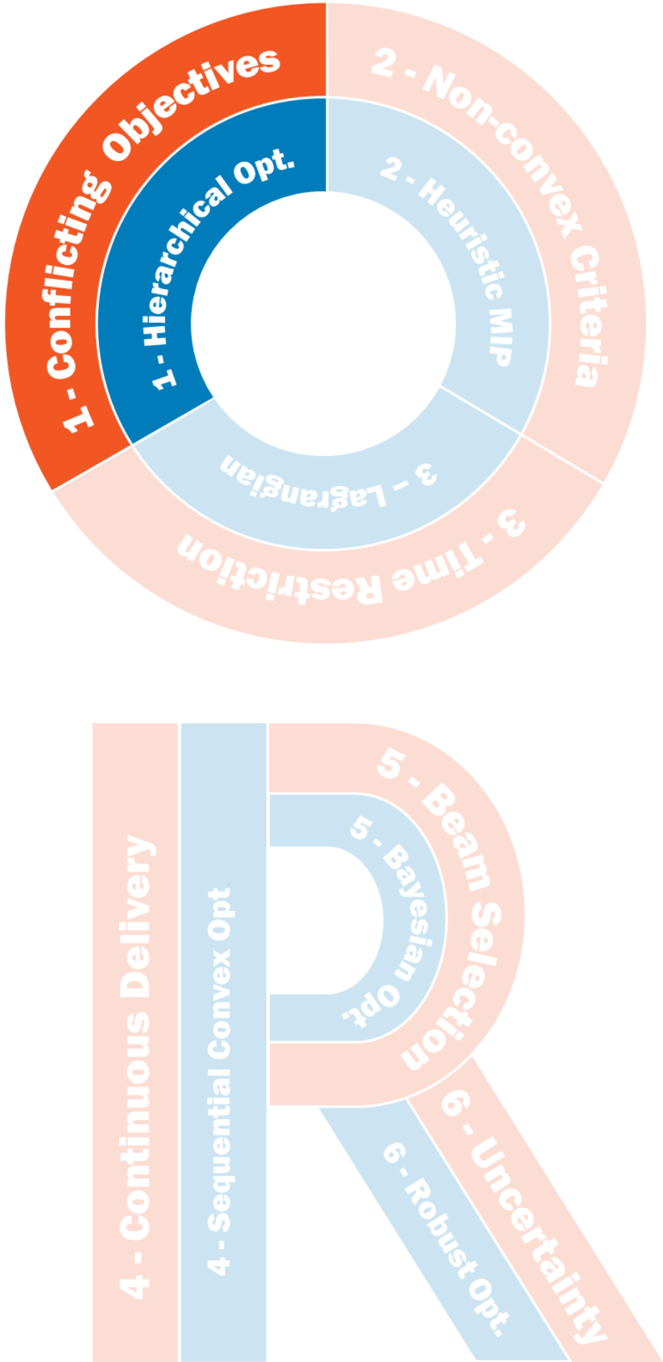


Challenges
OR Solutions
1 - Conflicting Objectives
2 - Non-convex Criteria
3 - Time Restriction
1 - Hierarchical Opt.
2 - Heuristic MIP
3 - Lagrangian
4 - Continuous Delivery
4 - Sequential Convex Opt.
5 - Beam Selection
5 - Bayesian Opt.
6 - Uncertainty
6 - Robust Opt.
Operations
(Clinically implemented)
Research
(Yet to be implemented)

Challenge 1: Conflicting Objectives

- **Challenge**
  - Conflicting objectives: tumor irradiation V.S. unintended nearby tissues irradiation
- **OR Solution**
  - Hierarchical constrained non-linear optimization

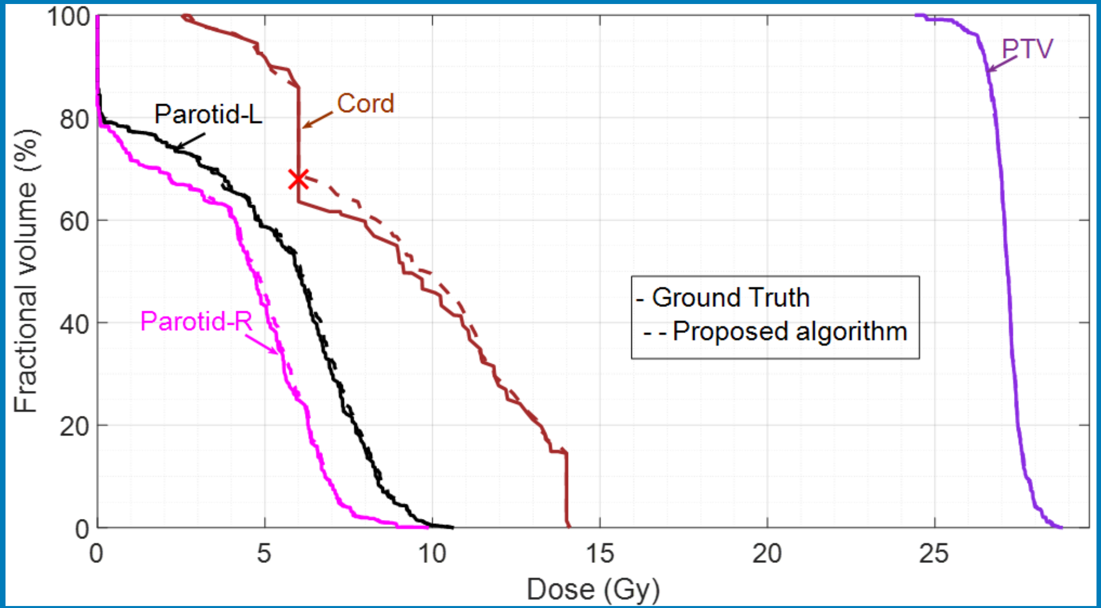




Publication: "Automated Intensity …...", Medical Physics, (2019)

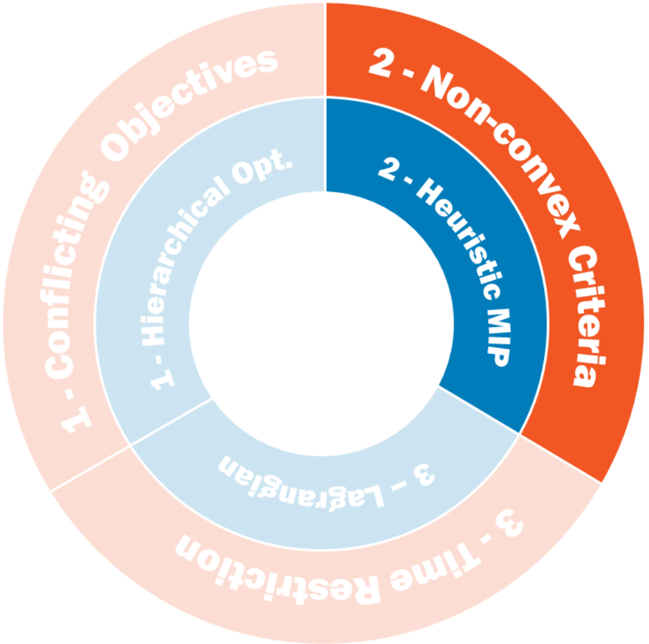
Challenge 2: Non-Convexity

- **Challenge**
  - Non-convex volume constraints resulting in MIP (e.g., at most 30% of lung should receive radiation dose more than 10Gy)
- **OR Solution**
  - Solving convex relaxation
  - An effective heuristic by exploiting the characteristics of the problem



MIP	Heuristic
~ 15 hrs	3 mins

Publication: “Integrating Soft …”, Medical Physics, (2019)



Challenge 3: Computational Challenge

- **Challenge**
  - Large-scale non-linear constrained optimization problems (> 100,000 variables and > 500,000 constraints).
  - Short clinical time frame (~ 1-2 hours)
  - Modeling limitations and inaccuracies
- **OR Solution**
  - Solving simplified constrained problems first
  - Incorporating the resultant inaccuracies later (Lagrangian problem)
  - Interior point method implemented in KNITRO/AMPL

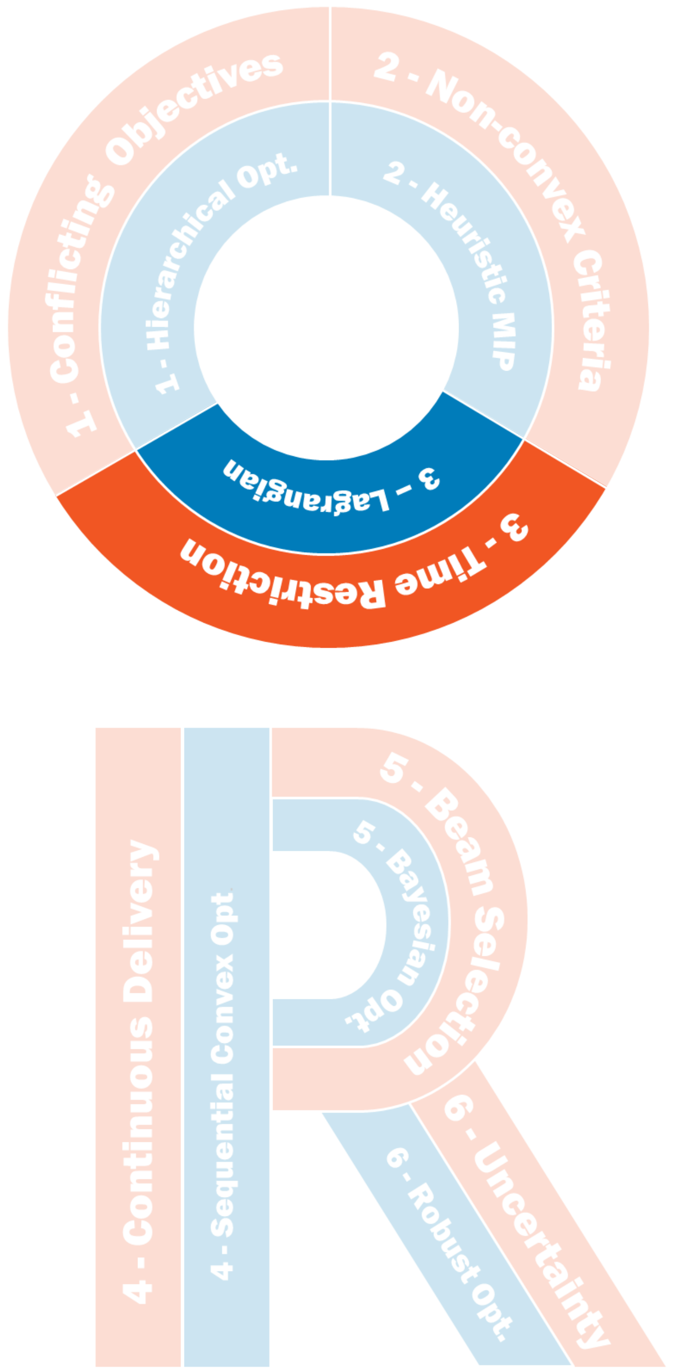
Step-C optimization problem (dose correction step):

$$\mathbf{Min}\ \mathbf{F_C(x)} = \mathbf{F_{II}(x)} + \sum_{k\in K} \boldsymbol{\lambda_k} \times g_k(\mathbf{Ax} + \boldsymbol{\Delta})$$

$$(\mathbf{C.1})\ \left\|\mathbf{x} - \mathbf{x^{II}}\right\|_2^2 \le \epsilon$$

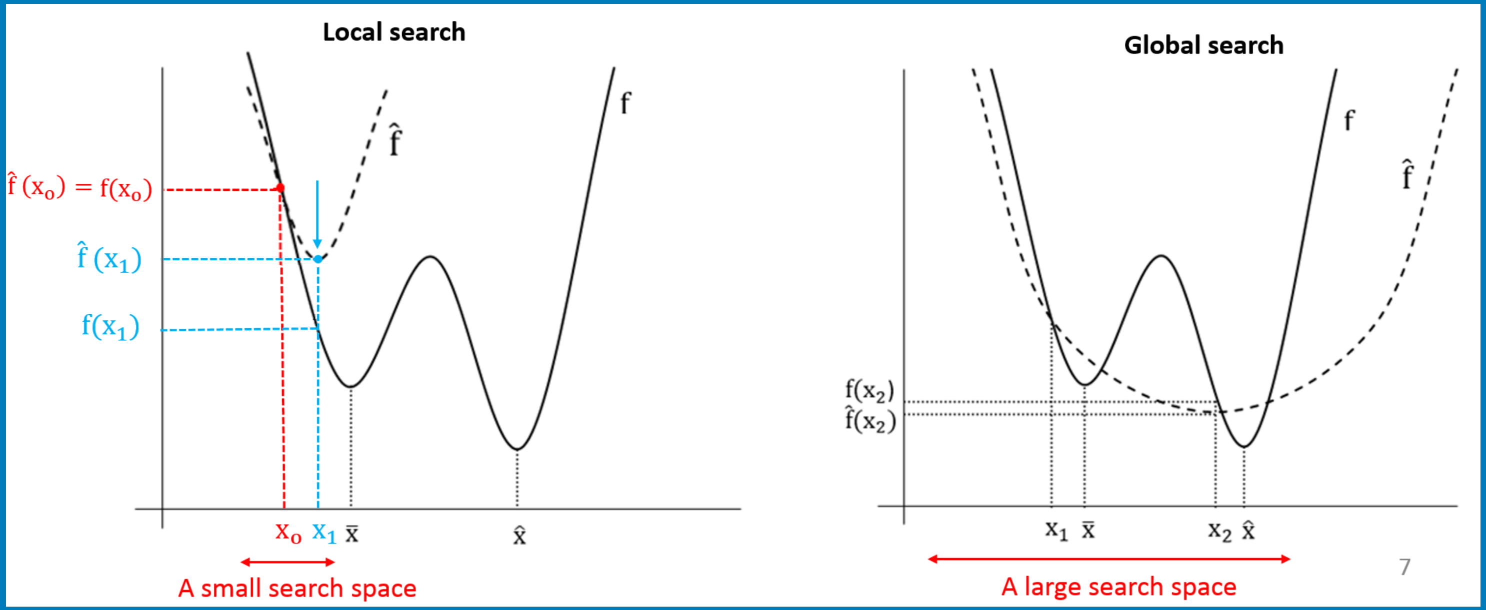
$$(\mathbf{C.2})\ \mathbf{x} \ge \mathbf{0}$$

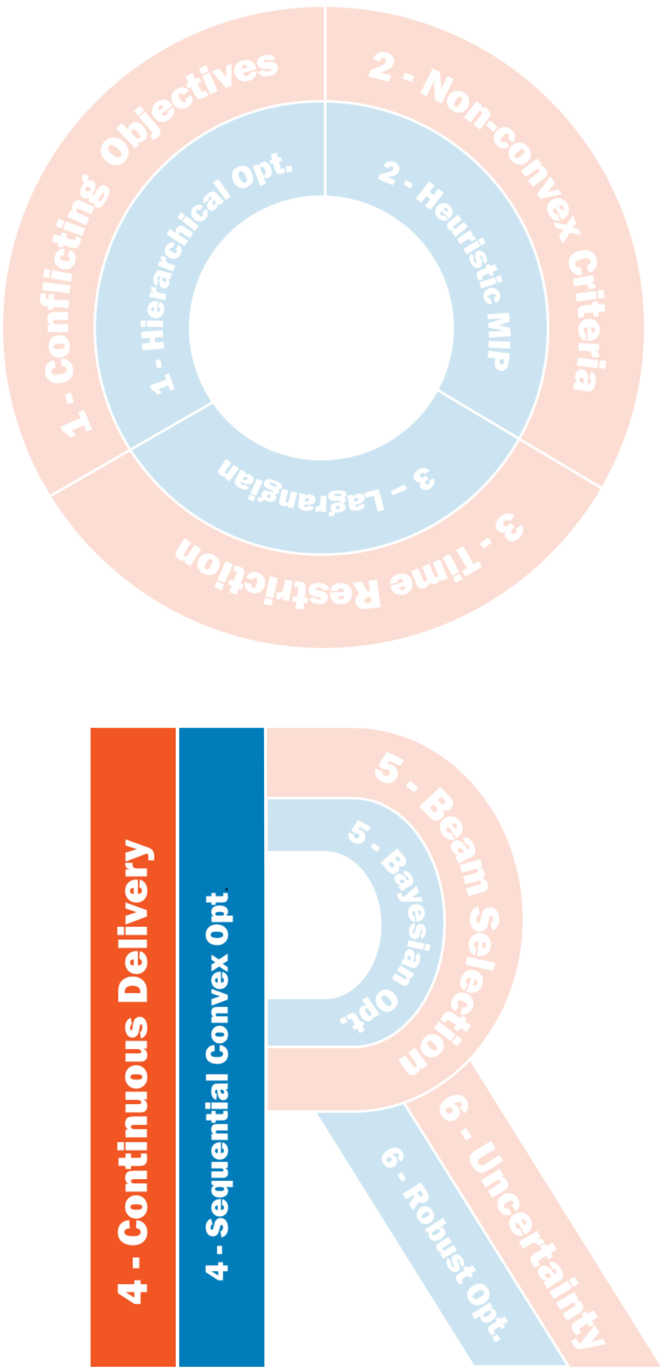
Publication: “Automated Intensity …...”, Medical Physics, (2019)



Challenge 4: Continuous Delivery (VMAT)

- **Challenge**
  - Highly non-convex large-scale optimization problem
- **OR Solution**
  - Sequential convex programming
  - Convex approximations by restricting MLC leaf movements

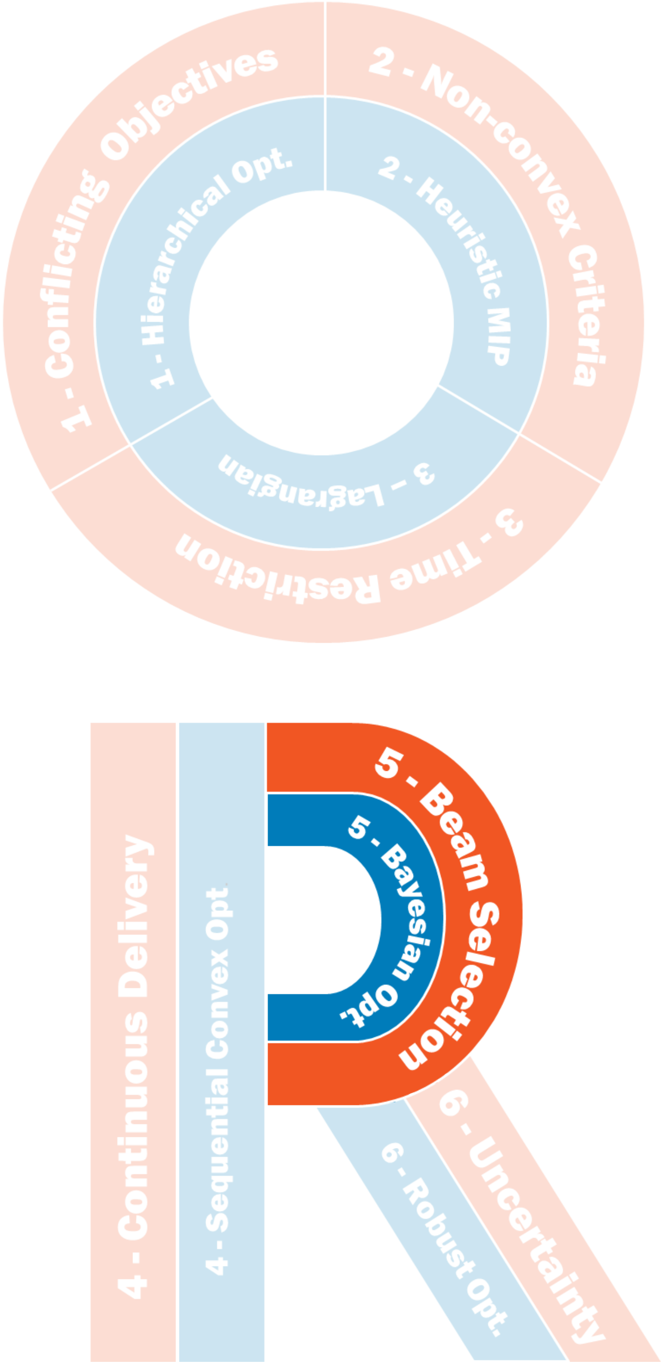




Publication: “Solving the Volumetric ….” Physics in Medicine and Biology, (2021)

Challenge 5: Beam Angle Selection (Proton)

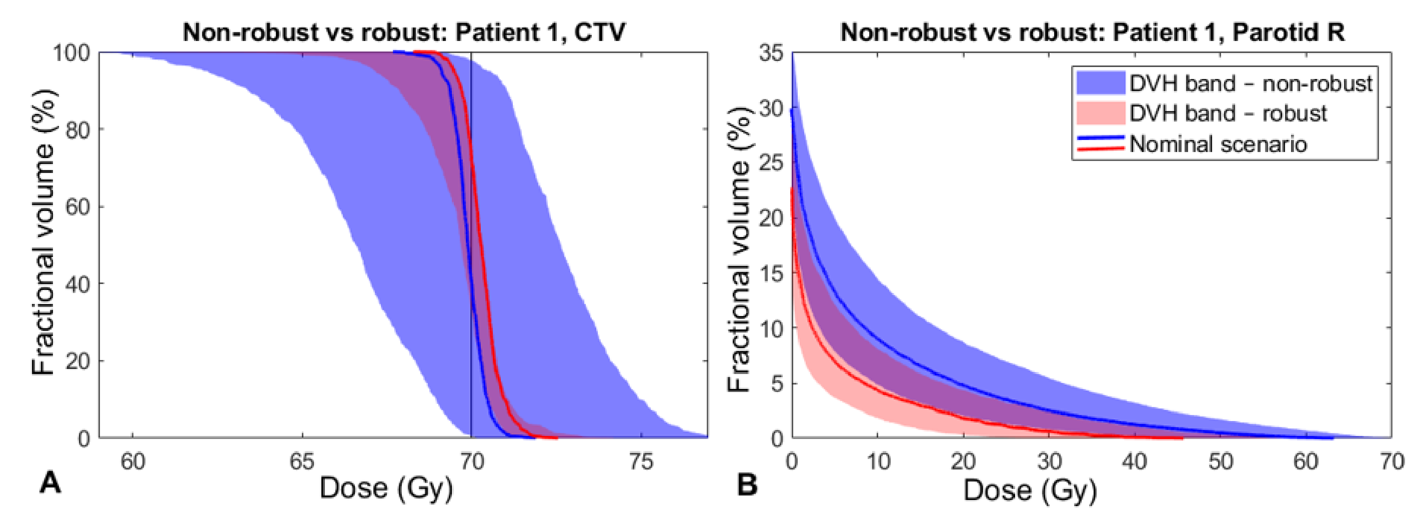
- **Challenge**
  - Computationally challenging combinatorial problem
- **OR Solution**
  - Bayesian Optimization (INFORMS 2018 tutorial)
  - < 4% of candidates evaluated before finding optimal solution



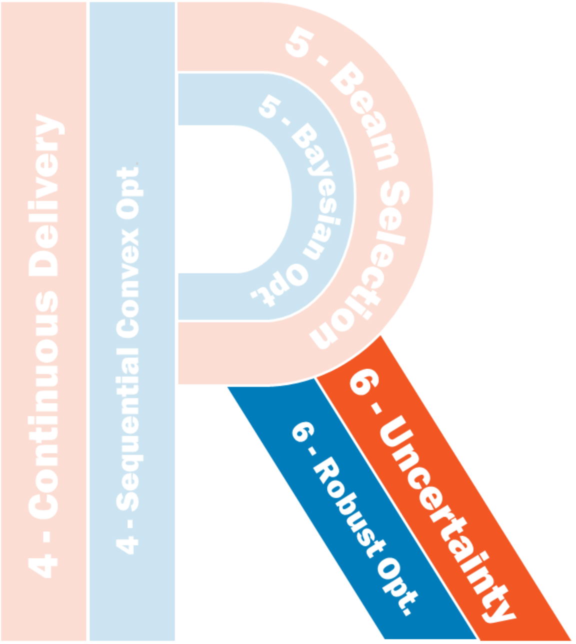
Publication: “Automating Proton Treatment Planning with Beam Angle…” Medical Physics, (2020)

Challenge 6: Uncertainty Management (Proton)

- **Challenge**
  - Uncertainty (patient set-up error, proton range uncertainty,..)
- **OR Solution**
  - Robust optimization
  - Using p-norm to control the level of robustness (between stochastic and worst-case)



Publication: "Automated Proton Treatment Planning with Robust Optimization." Medical Physics,(2020)

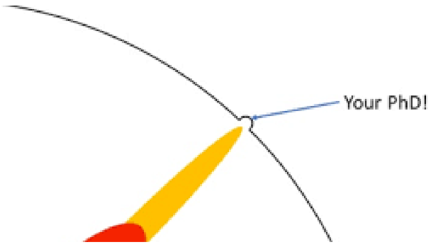


Science contributions

- **Building on OR tools already applied in radiation therapy**
  - Mathematical modeling of radiation and physics
  - Hierarchical constrained optimization (Medical Physics, 2019)
  - Robust optimization (Medical Physics, 2020)
  - Mixed integer programming (Medical Physics, 2019)

- **Identifying OR tools never applied in radiation therapy**
  - Bayesian Optimization (Medical Physics, 2020)
  - Sequential convex programming (PMB, 2021)

- **Pushing the boundaries of OR**
  - Lagrangian to correct modeling inaccuracies (Medical Physics, 2019)
  - Customized sequential convex programming (PMB, 2021)
  - Heuristic (MIP + application domain knowledge) (Medical Physics, 2020)



- **A home-grown OR technique part of the clinical routine**

Publications and Patents

Peer-reviewed publications

1) "Automated Intensity Modulated Treatment Planning: The Expedited Constrained Hierarchical Optimization (ECHO) System." **Medical Physics, (2019)**

2) "Clinical Experience of Automated SBRT Paraspinal and Other Metastatic Tumor Planning With Constrained Hierarchical Optimization." **Advances in Radiation Oncology, (2019)**

3) Integrating Soft and Hard Dose-Volume Constraints into Hierarchical Constrained IMRT Optimization, **Medical Physics, (2019)**

4) "Automated Proton Treatment Planning with Robust Optimization Using Constrained Hierarchical Optimization." **Medical Physics, (2020)**

5) "Automating Proton Treatment Planning with Beam Angle Selection Using Bayesian Optimization." **Medical Physics, (2020)**

6) "Solving the Volumetric Modulated Arc Therapy (VMAT) Problem Using a Sequential Convex Programming Method." **Physics in Medicine and Biology, (2021)**

7) **"**IMRT treatment planning based on prioritizing prescription goals". **Physics in Medicine and Biology, 2007**

8) "IMRT treatment planning for prostate cancer using prioritized prescription optimization and mean-tail-dose functions". **Linear Algebra Appl. 2008**

Patents

1) A method for radiotherapy automatic treatment planning using Expedited Hierarchical Constrained Optimization (ECHO)

2) Methods and systems for automated volumetric modulated arc therapy (VMAT) for external radiation therapy

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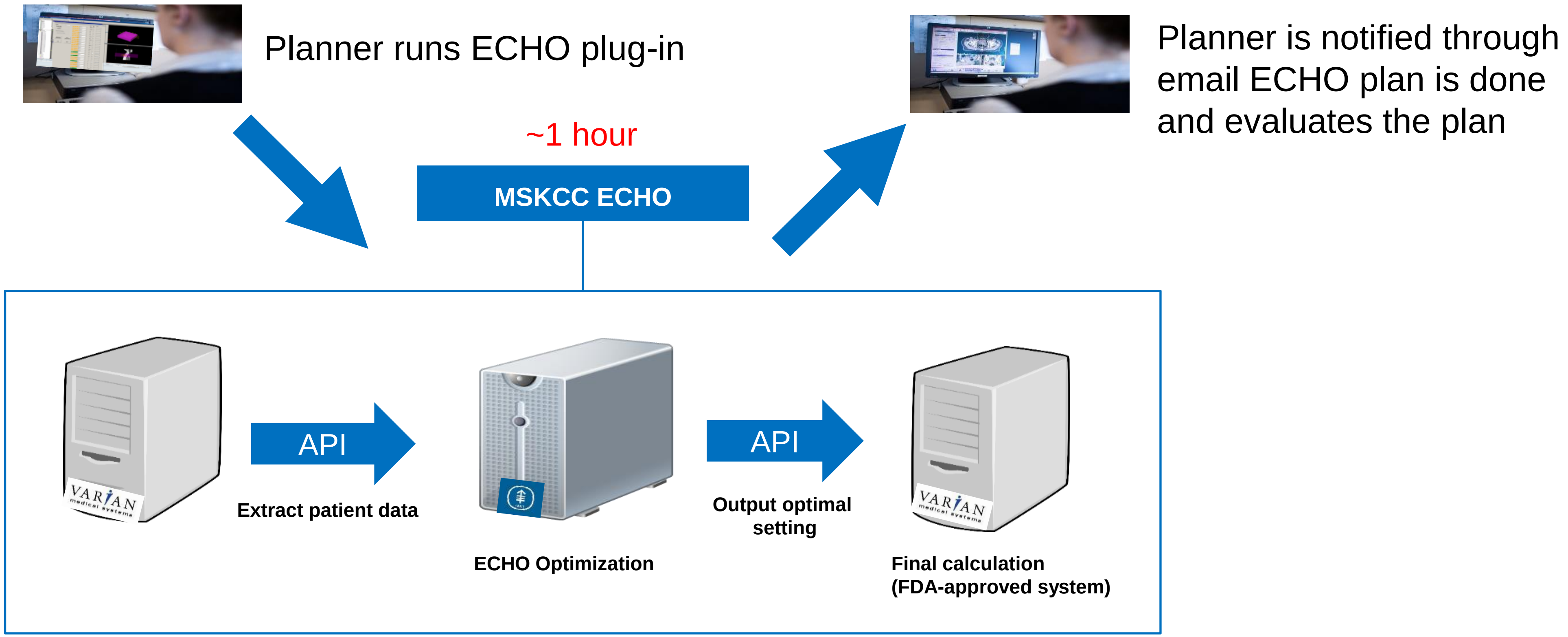
Clinical implementation

- Integrated with the FDA-approved Varian Eclipse® Treatment Planning System

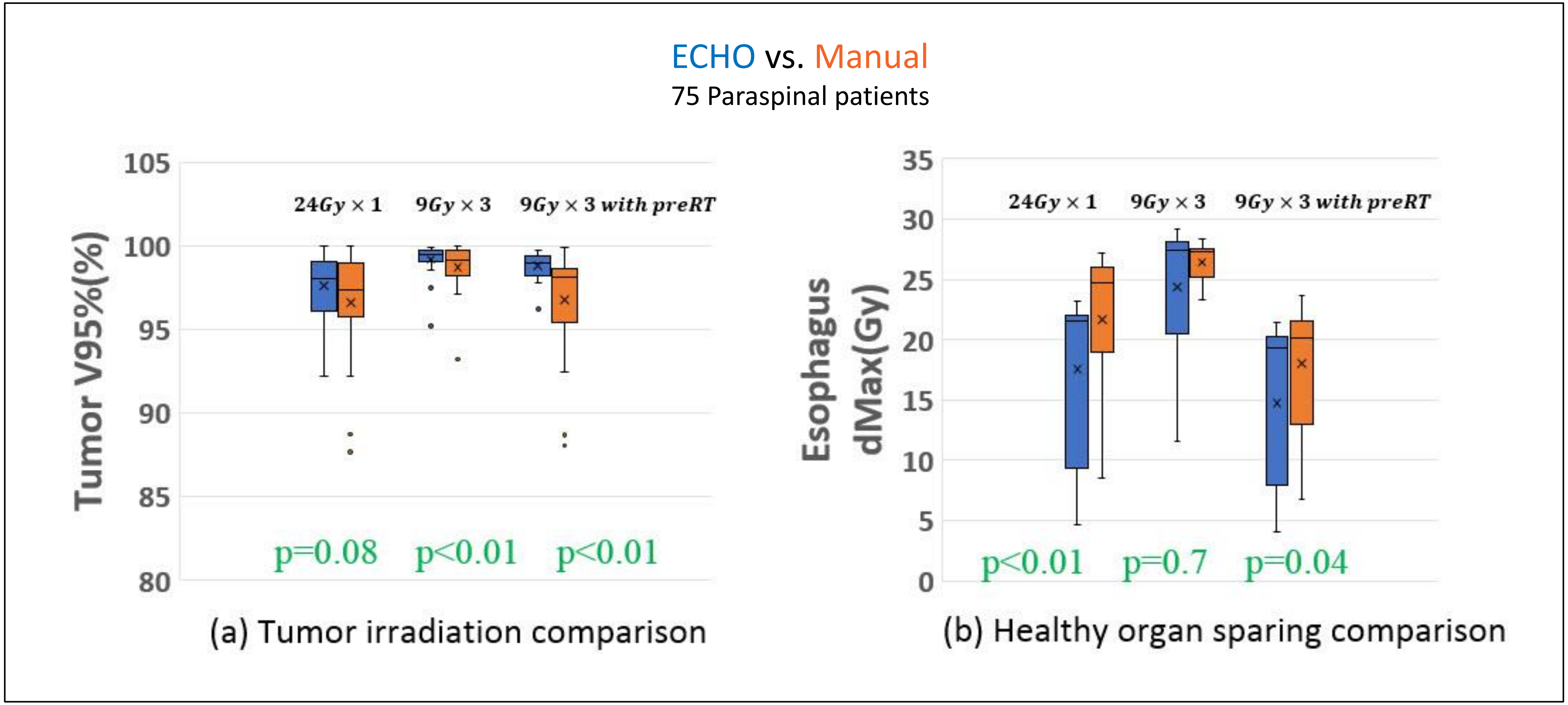


Clinical Rollout

- Not the same as regular software rollout
  - ECHO has a huge impact on patient care
- Pre-clinical validation (plans are superior/comparable)
  - For each prescription within each site due to variability of clinical criteria
- Rigorous QA process to ensure safe delivery
  - Measurements & analysis before treatment

Pre-Clinical Validation

- Pre-clinical study before each clinical release
- ECHO plans superior or comparable to the manual plans

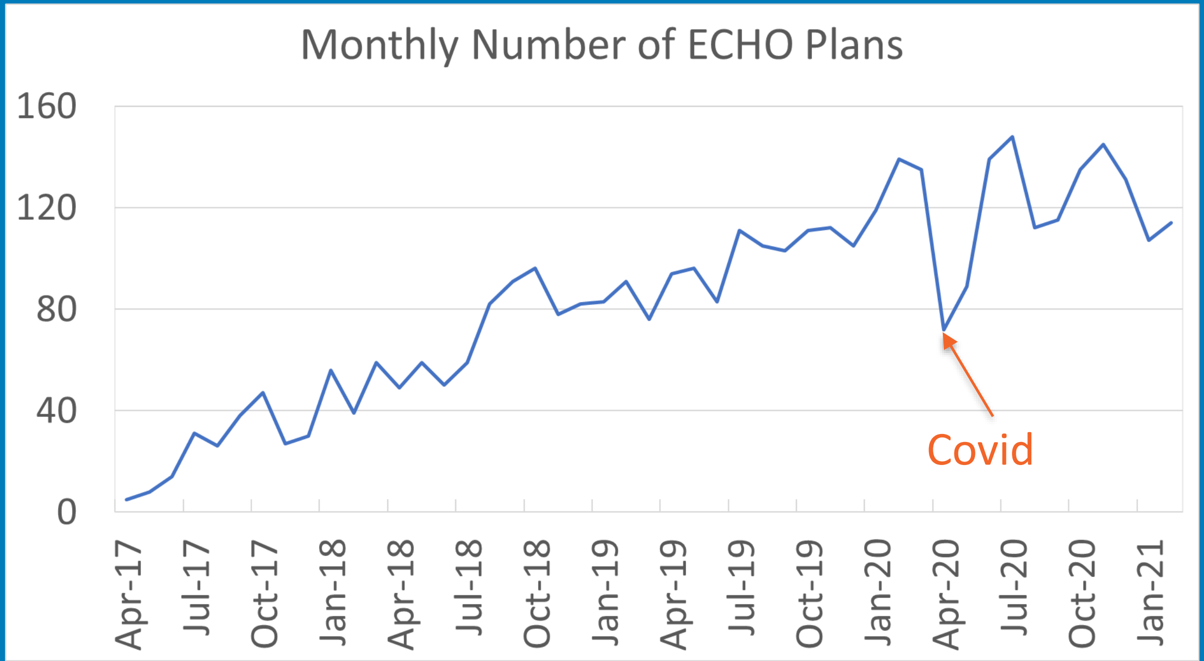


Safe Delivery

- Final calculations in FDA-approved system
- Rigorous clinical QA protocols

Clinical Implementation

- ECHO in clinical use since Apr-2017
- > 3000 treated patients
  (Paraspinal/Other Metastatic Tumors, Prostate, Head-and-Neck, Lung)
- Automation with ECHO plans more important during COVID
- ECHO plans steadily increasing, accounting ~ 15% of all plans
- Expecting to treat ~ 80% by the end of 2022



Potential Global Impact

- > 75% countries lack qualified planners (according to IOMP)
    - a platform to share institutional knowledge

- ECHO is transportable
    - Integrated with widely-used planning system (Eclipse®)
    - Clinical criteria customizable
    - Potential integration with other planning systems

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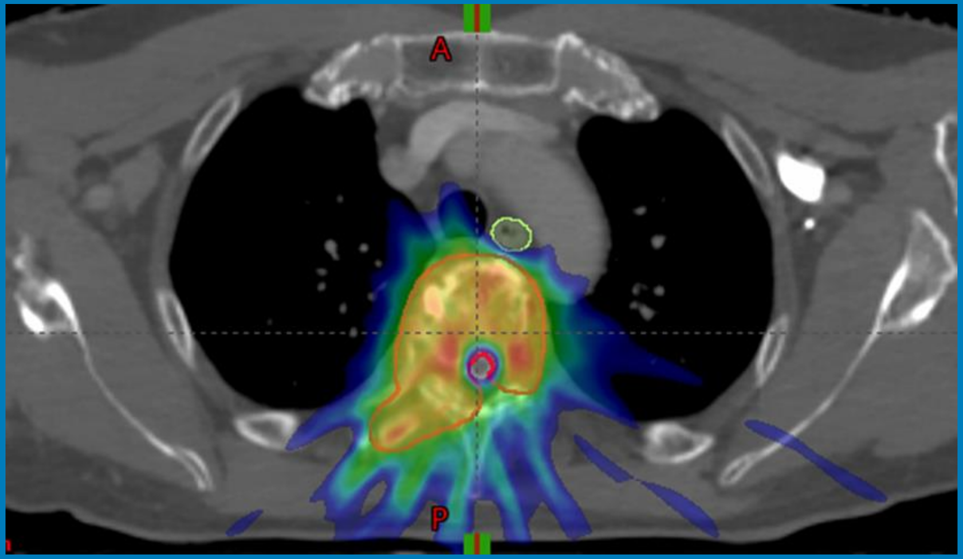
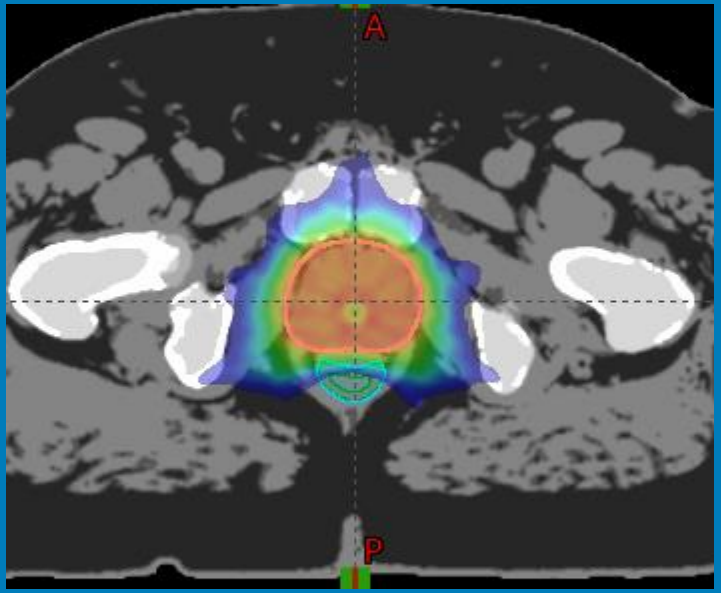
Clinical Impact

- No more trial-and-error (Rene)
- Flexible (Alex)
- Easy plan checking (Ying)
- Less stressful expedited planning (Niral)





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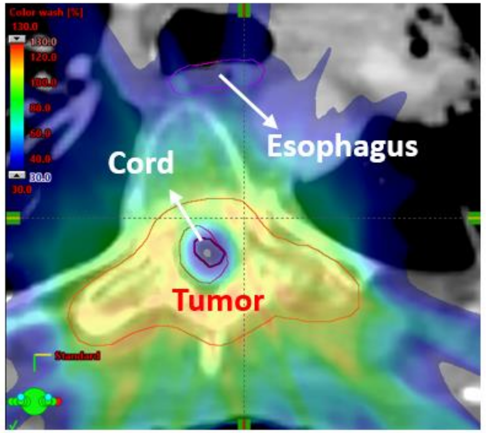
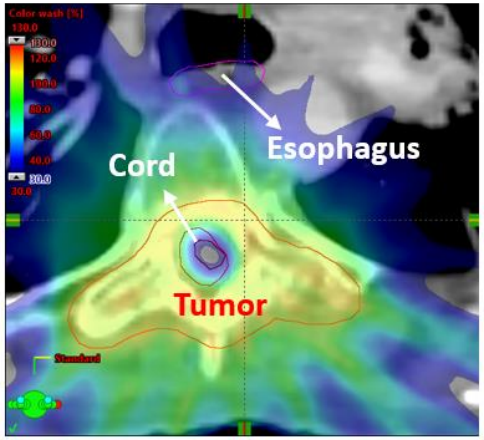
Patient Impact

- > 2000 spine patients treated with ECHO
- Spine tumor treatment is often time sensitive
  - Severe Pain
  - Spinal cord compression
- Better patient experience
  - Same day treatment for patients in urgent need
  - Pre-operative radiation
  - Reduce unnecessary surgery
  - Reducing hospital stays



Manual



ECHO

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