EMORY
PROTON THERAPY CENTER
WINSHIP CANCER INSTITUTE

DEBATE: Proton Therapy is Superior to IMRT in the Definitive Radiation Therapy Setting

(H&N Edition)

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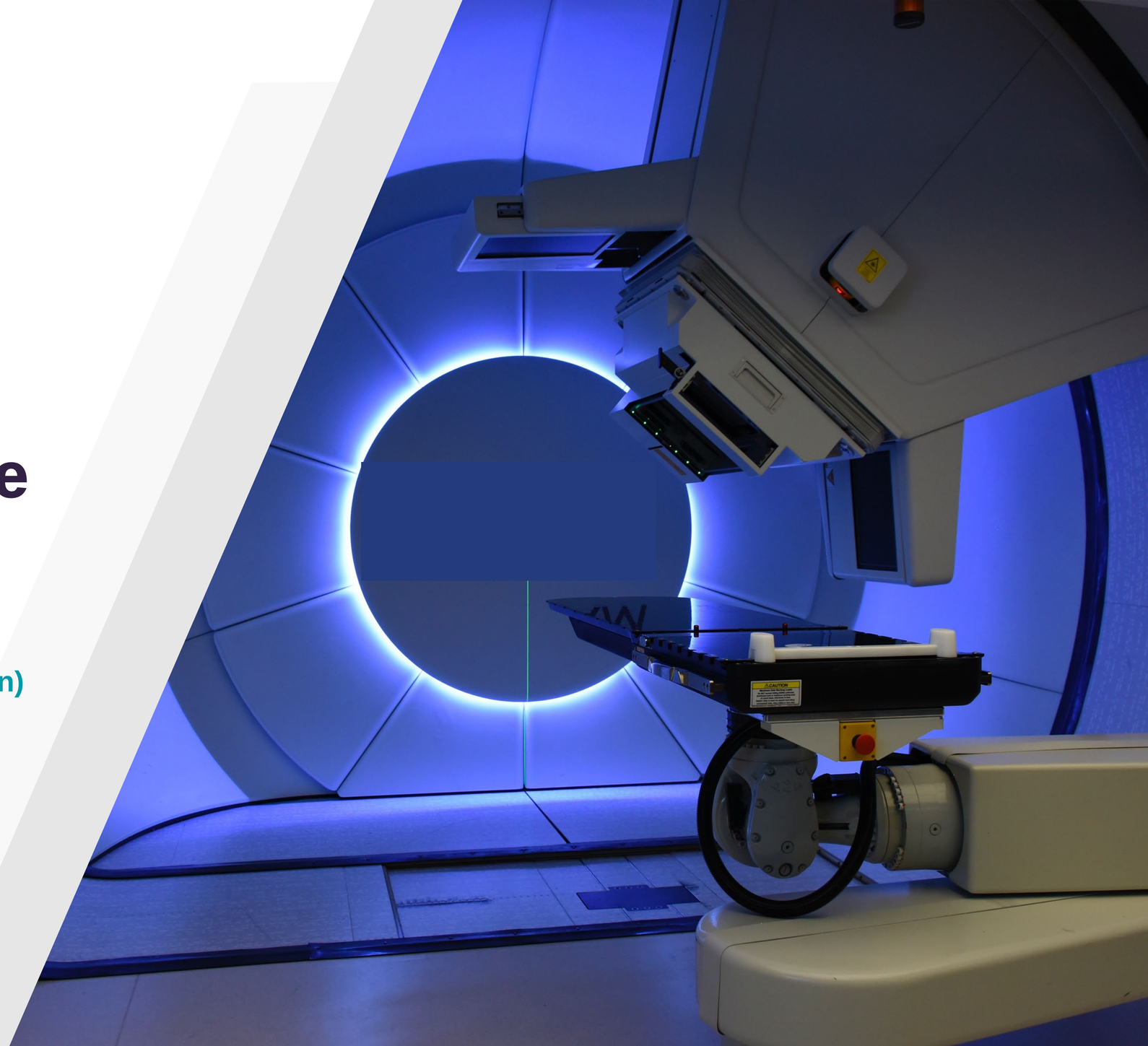

Disclosures

Dr. Stokes

No relevant financial relationships to disclose.
Presentation and discussion will not include off-label or unapproved product usage.

Dr. McDonald

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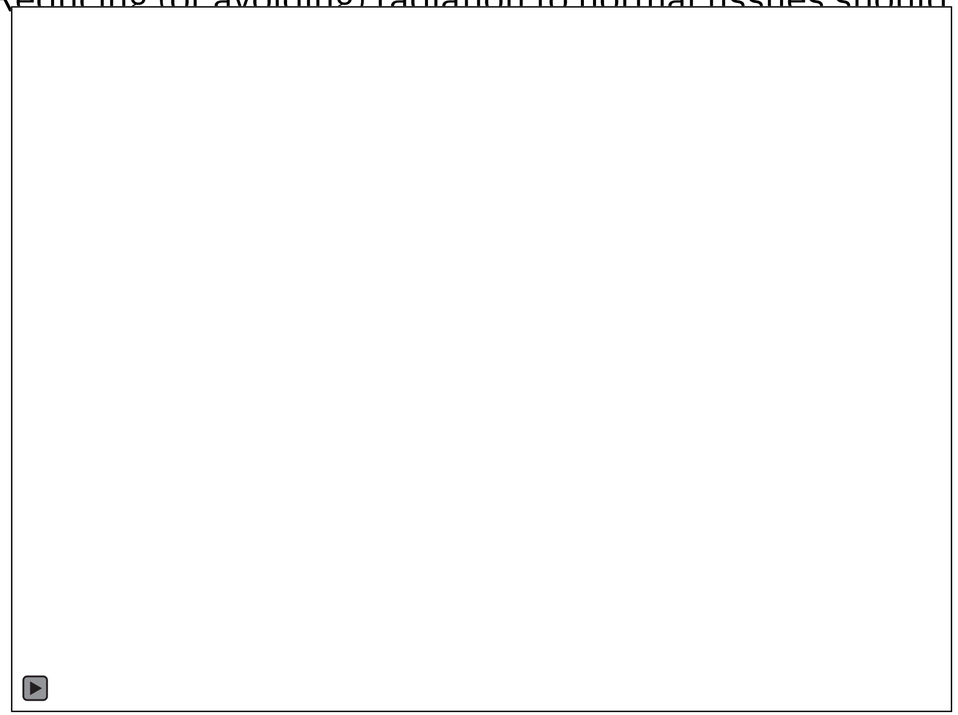
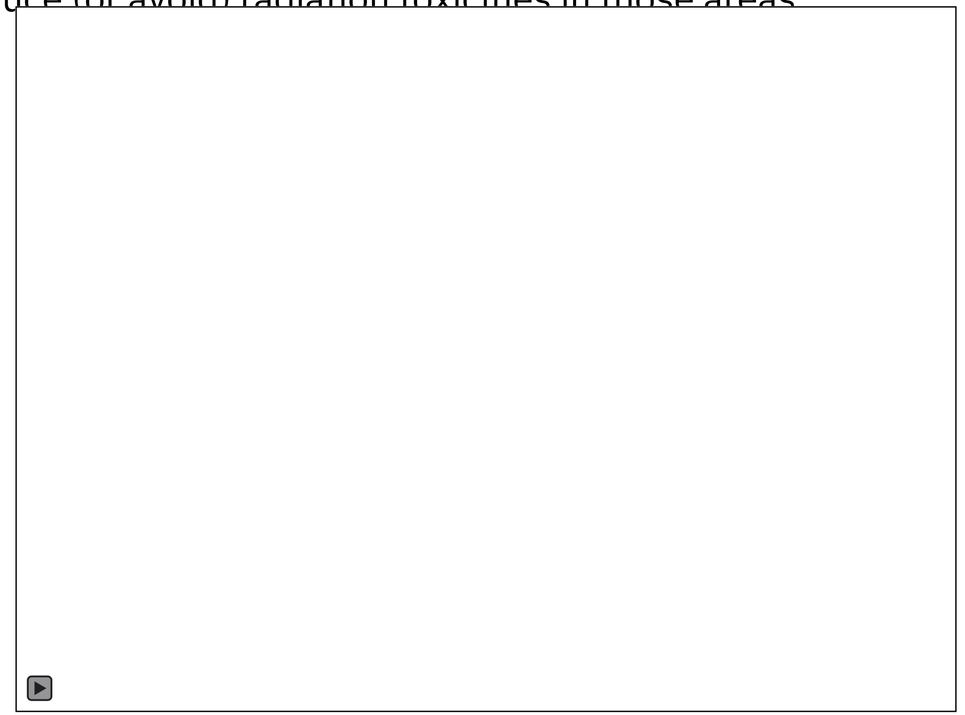
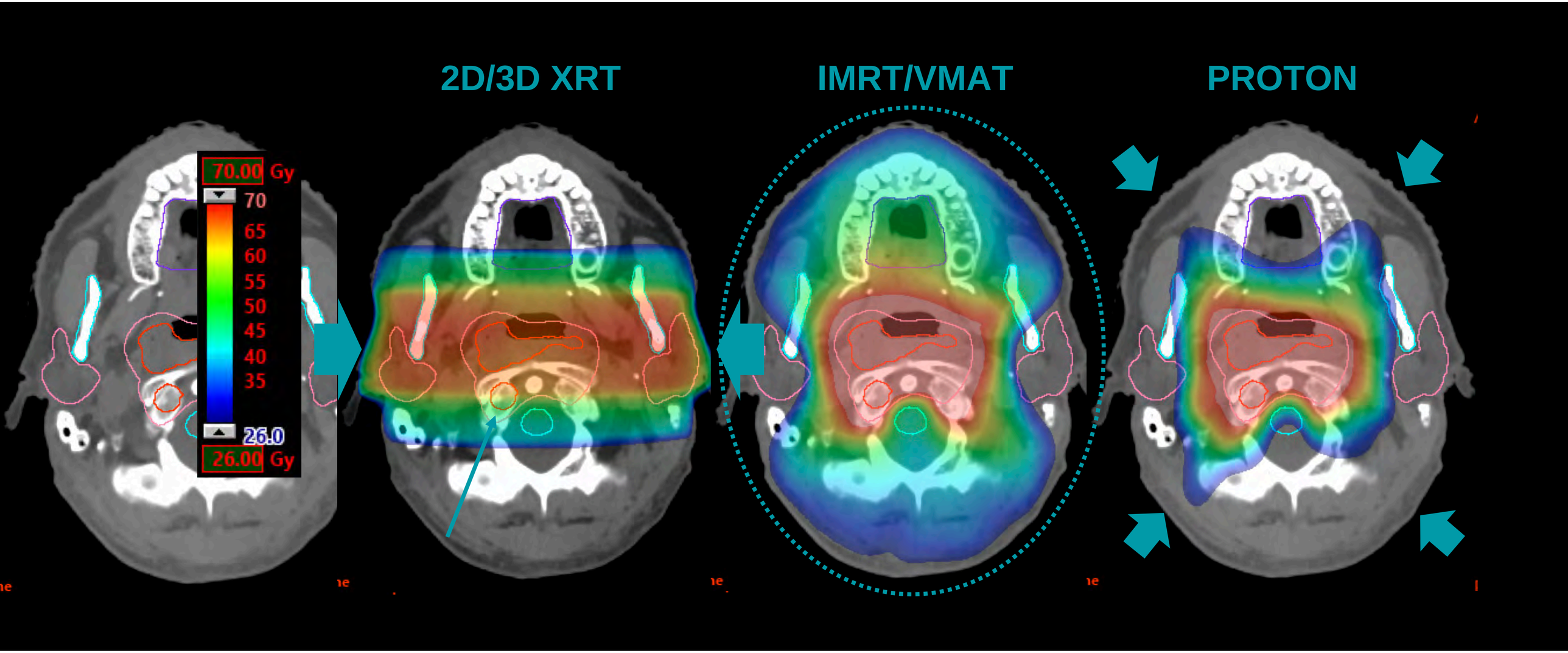
Proton Therapy

- Ionizing radiation delivered via proton particles rather than x-rays (photons)
- Unlike x-rays, protons have a finite range. After treating the tumor, they stop
- Same target treated to same dose, but nontarget normal tissues receive less (or no) radiation
- Reducing (or avoiding) radiation to normal tissues should reduce (or avoid) radiation toxicities in those areas

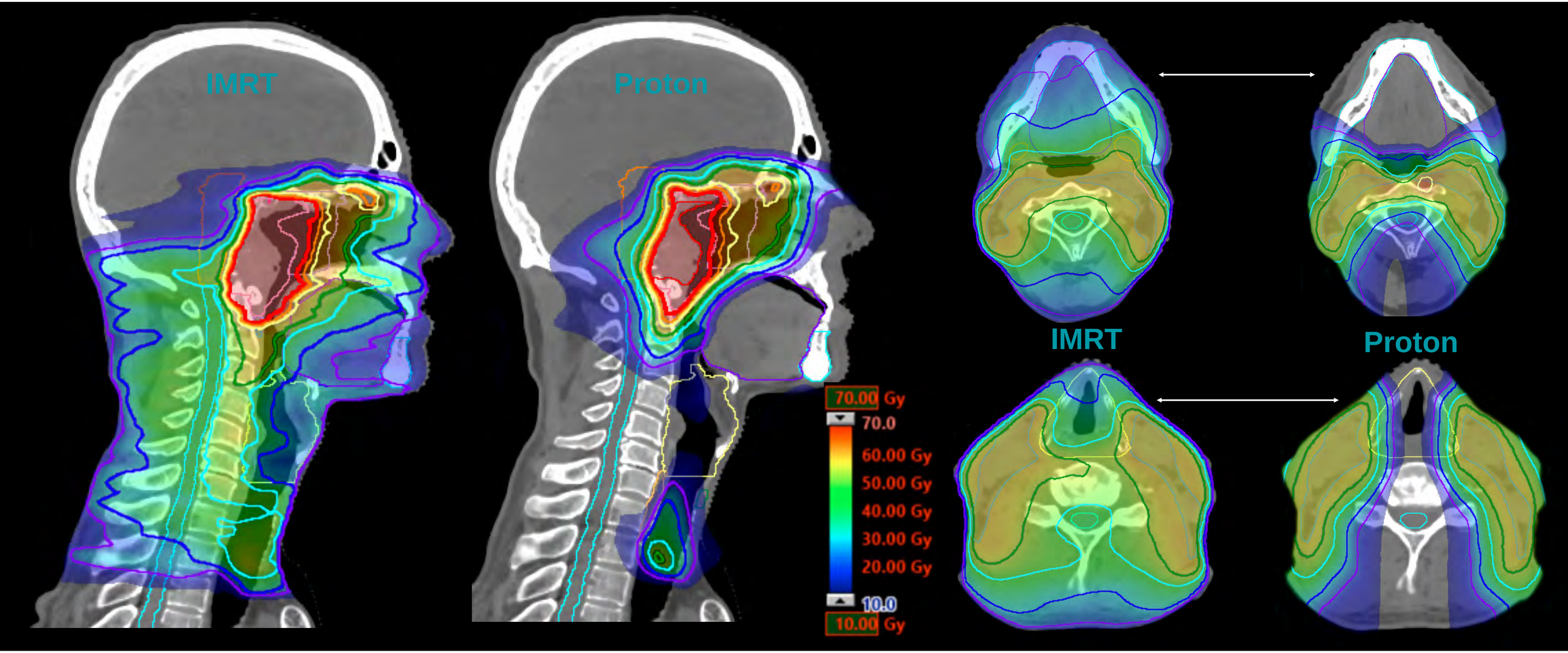




Radiation Evolution



Nasopharyngeal Cancer



Data

What data do we have for proton therapy?

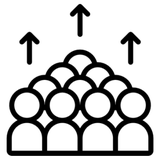
Treatment Planning Comparison Studies

Innumerable studies in many disease sites
Proton therapy reduces radiation to nontarget normal tissues often with a predicted reduction in risk of toxicities

Retrospective Cohort Comparisons (vs IMRT)

Many studies with consistent themes. Some examples in H&N:
[1] MSKCC, Nasopharynx: significantly fewer G2+ acute toxicities
[2] Taiwan, Nasopharynx: significantly reduced need for NG tube and decreased weight loss
[3] MSKCC, Parotid: significant less G2+ mucositis, dysgeusia, or nausea
[4] MDACC, Oropharynx: lower risk of G3 weight loss and a 50% reduction in need for g-tube
[5] Mayo, Oropharynx: lower incidence of g-tube placement, less often hospitalized after treatment, less likely to need narcotic pain medications
[6] U Penn: Varied Sites: significantly fewer G2+ acute toxicities, reduced unplanned hospitalizations, less likely to experience a decline in PS

Fewer toxicities while Disease control at least as good as IMRT



Big(ger) Data

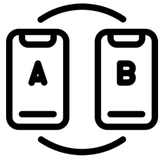
[7] NCDB: proton therapy a/w reduced secondary malignancy risk, OR=0.31
[8] Metanalysis, Paranasal sinus: proton therapy a/w improved DFS and LC

[1] PMID 34143193
[2] PMID 34298769
[3] PMID 26867969
[4] PMID 27342249
[5] PMID 32234612
[6] PMID 31876914
[7] PMID 32426866
[8] PMID 24980873

Data continued

Patient Reported Outcomes (vs IMRT)

[1] Mayo: oropharyngeal pts treated w/ proton therapy reported less cough, less dysgeusia, feeling less ill, and reported better swallow function
[2] MDACC: oropharyngeal pts treated w/ proton therapy reported lower total symptom burden in first 3 months after treatment
[3] U. Penn: postoperative oropharyngeal pts treated w/ proton therapy reported better QOL at 6 and 12 months after radiation in areas including xerostomia, pain, and physical function



Randomized Controlled Trials

RCT (MDACC-led) of IMRT versus Proton Therapy in Oropharyngeal Cancer treated with chemoRT – completed accrual. Primary endpoint = PFS
At least 4 other ongoing RCTs in H&N cancer
[4] MDACC: oropharyngeal pts randomized to treatment w/ proton therapy were significantly more likely to return to work after treatment, and reported reduced work impairment compared to IMRT
[5] RCT in Esophageal Cancer: proton therapy reduced total toxicity burden, reduced postoperative complications, reduced G4 lymphopenia
[6] RCT in GBM: proton therapy reduced G2+ toxicities with lower patient-reported fatigue

How many RCTs were conducted in the USA comparing IMRT to older radiation?

0

How many RCTs have demonstrated improved OS with IMRT for H&N?

0

[1] PMID 32234612
[2] PMID 27354125
[3] PMID 26867969
[4] PMID 34285958
[5] PMID 32160096
[6] PMID 33647972

Cost

Cost

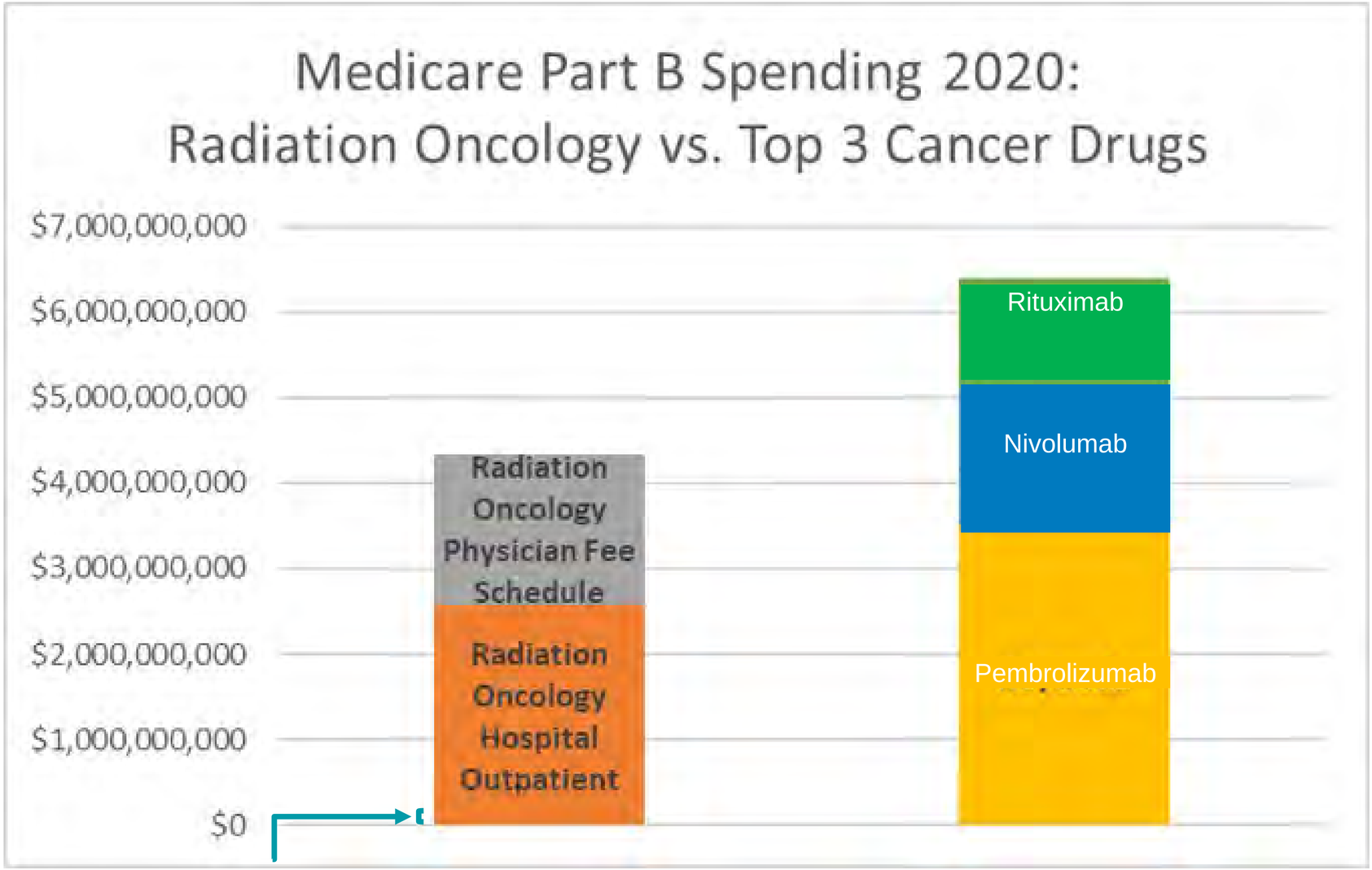
…to the Patient

- Out-of-pocket costs are equal between PBT and IMRT.
- Most patients reach their out-of-pocket maximum in the year they receive radiotherapy.

…to the Payor

- This will likely be higher with PBT than with IMRT…
- …but this upfront cost neglects potential downstream savings from reduced health care utilization as a result of reduced toxicity.

Some context…



PBT accounts for ~2% of all radiotherapy charges

Cost

Time Toxicity

- Improvements in outcome may come at the cost of significant time in health care facilities (away from home).

The "Time Toxicity" of Cancer Treatment

Time Toxicity — Time spent coordinating treatments and in-visits to a health care facility (including travel and waiting), seeking urgent/emergent care for side effects, hospitalizations, and follow-up tests and rehabilitation.

Proposed Metric of Time Toxicity — Days with Physical Health Care System Contact

(a 1-hour lab visit = a 6-hour infusion = a 12-hour urgent care visit = an overnight hospitalization; all these are "all-day affairs")

Overall survival = **Days With Physical Health Care System Contact** + **Home Days**

Hypothetical Treatment	Clinical Trajectory	Overall Survival (in days)	Home Days
Option A (Chemotherapy)	Frequent clinic visits; Chemotherapy toxicity, hospitalization, and rehabilitation	150	90
Option B (No cancer-directed treatment)	Short hospitalization for symptom control	120	115

Day 0 — Day 30 — Day 90 — Day 180

With information on **"Time Toxicity"** and **"Home Days"**, a clinician can better guide a patient regarding a treatment strategy that best aligns with the patient's goals.

Gupta *JCO* 2022

Cost

Time Toxicity

- PBT and IMRT are broadly similar in number of visits:
  - 1 consultation
  - 1 simulation
  - 30-35 treatments

- But PBT entails longer visit duration and more time in the radiotherapy facility:
  - each treatment may take longer (30+ minutes vs 15 minutes)
  - QA scans
  - proton beam downtime

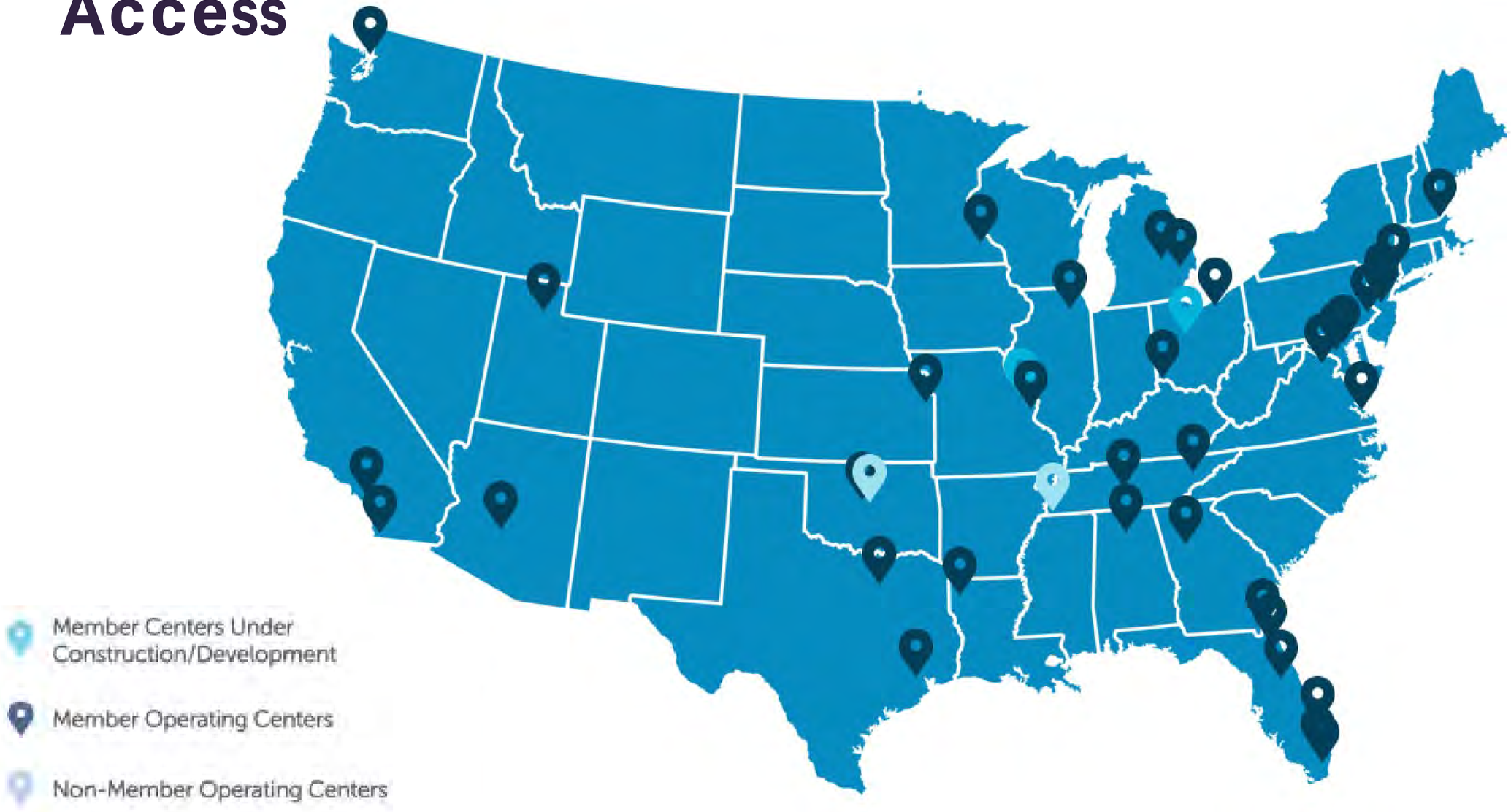
- PBT may require relocation away from home, family, and employment.

Cost

Increased cost of PBT must be justified by anticipated benefit.

Access

Access



NAPT: *proton-therapy.org/map,* accessed June 2022

Access

Who Receives Proton Therapy?

NCDB, 2004-2017

177,373 patients with HNC receiving radiotherapy

<1% received PBT

Evaluated **predictors** of receiving PBT.

McCall, *Multidisciplinary H&N Cancer Symposium* 2022

Access

Who Receives Proton Therapy?

Covariate	OR	(95%CI)
Race (vs White)		
Black	0.72	(0.55-0.95)
Hispanic	0.46	(0.31-0.68)
AIPI	0.87	(0.63-1.18)
Income Quartile (vs lowest)		
2nd	1.24	(0.96-1.60)
3rd	1.52	(1.17-1.97)
highest	2.07	(1.57-2.74)
Payor (vs Private Insurance)		
Medicare	0.99	(0.87-1.13)
Medicaid	0.41	(0.29-0.56)
Uninsured	0.36	(0.19-0.65)
Other	0.36	(0.21-0.63)
Facility Type (vs Academic)		
Community	0.19	(0.11-0.30)
Comprehensive Community	0.28	(0.23-0.34)
Integrated Network	0.50	(0.40-0.63)
Distance from Facility		
continuous (per 50 miles)	1.06	(1.05-1.07)

OR>1 indicates greater odds of receiving PBT

Additional variables evaluated in model:
year, age, education, population density, comorbidity score, primary site, histology, stage, systemic therapy, surgery, geography, volume

McCall, *Multidisciplinary H&N Cancer Symposium* 2022

Access

The best treatment is one that is broadly available.

Unfortunately, PBT is inaccessible by a majority of the US population.

Patients who will receive PBT must be fortunate enough to have the trifecta:

1) Awareness
2) Payor
3) Geography (or means to relocate for 6+ weeks)

Access & Clinical Trials

NCTN Cooperative Group Trials for HNC

non-metastatic, curative-intent, no prior radiotherapy

Study	Open at Emory ?	PBT Allowed ?
EA3132		
EA3161		
EA3163		
NRG HN001		
NRG HN004		
NRG HN005		
NRG HN006		
NRG HN008		
NRG HN009		
RTOG 1216		

Access & Clinical Trials

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EA3163	YES	
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NRG HN004	YES	
NRG HN005	YES	
NRG HN006	YES	
NRG HN008	YES	
NRG HN009	NO	
RTOG 1216	YES	

Access & Clinical Trials

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NRG HN004	YES	NO
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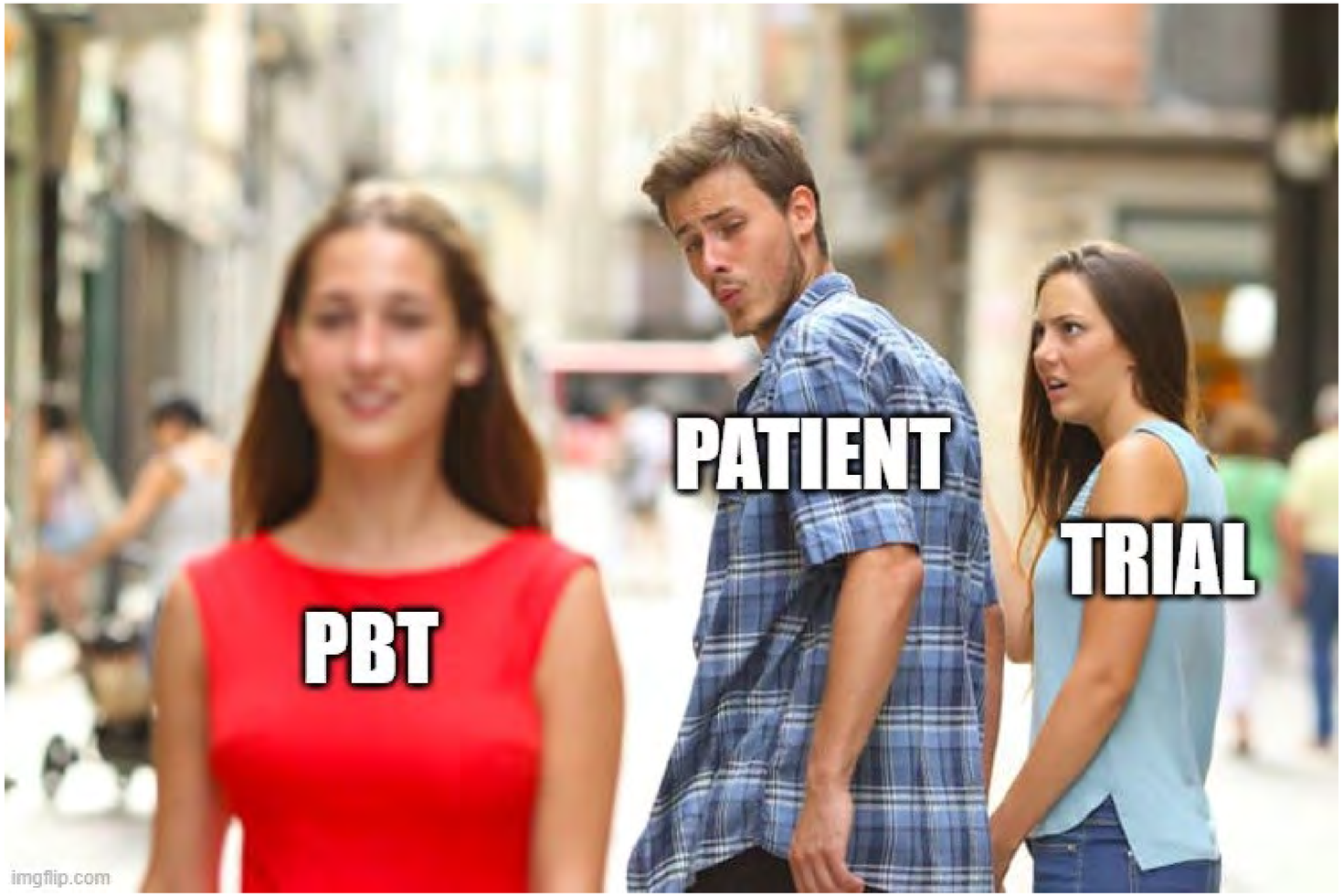
NRG HN006	YES	NO
NRG HN008	YES	NO
NRG HN009	NO	YES
RTOG 1216	YES	NO

Access & Clinical Trials



Access & Clinical Trials

Patient Selection

ASTRO Model Policies

PROTON BEAM THERAPY (PBT)

"Group 1" Indications

Conditions where published clinical data and medical necessity requirements frequently support the use of proton beam therapy, include (pertinent to H&N):

- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Tumors that approach or are located at the base of skull
- Re-irradiation cases

Patient Selection

The Worst Cases

- Cannot safely treat with IMRT

The Class Solution

- Proton therapy is consistently compelling and/or recognized as preferred
  - Nasopharynx
  - Paranasal Sinuses
  - Skull base tumors
  - Parotid
  - Reirradiation (when reRT appropriate)

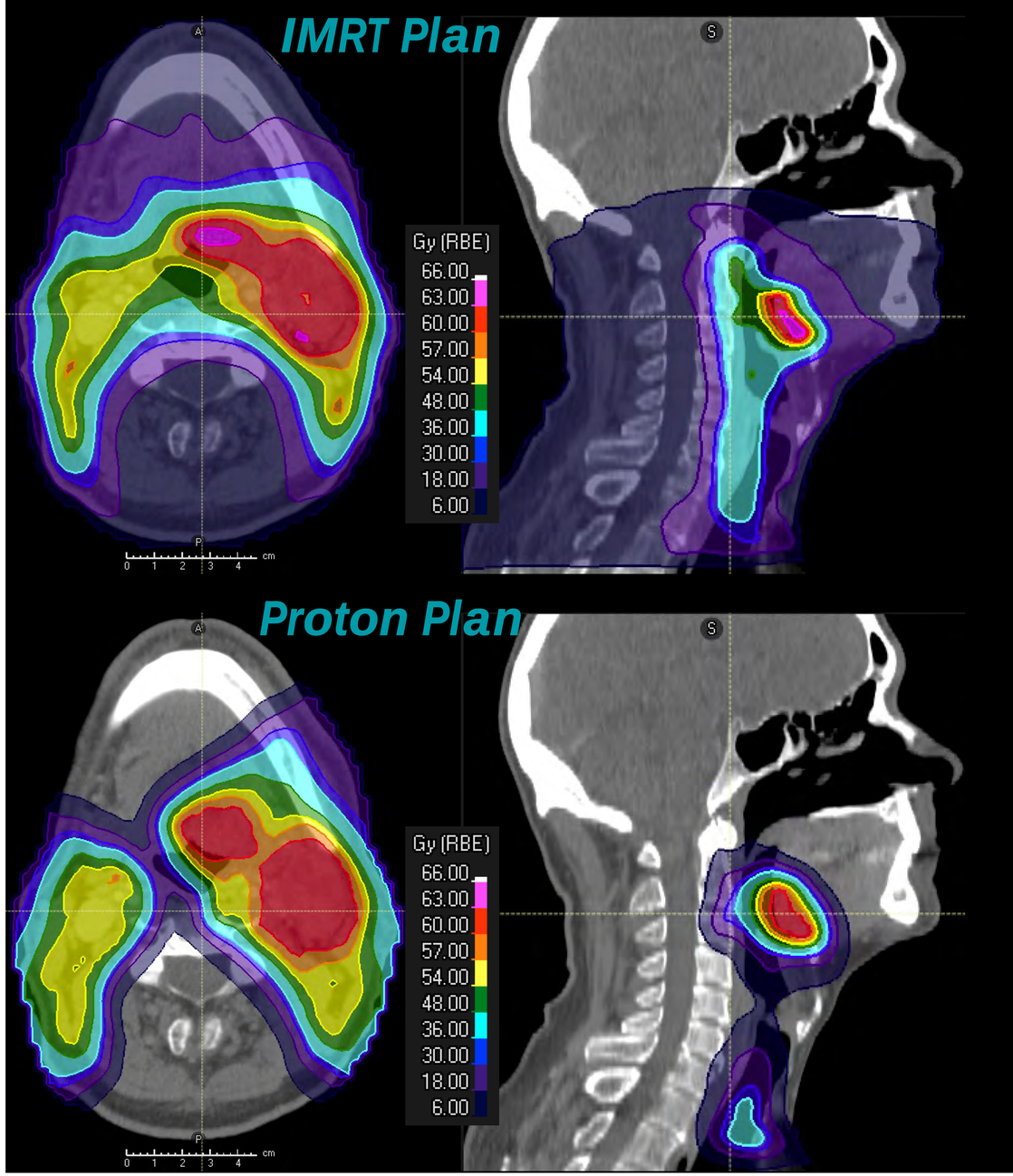
Individualized Medicine

- Compare competing radiation options in individual patients
- Use existing models to predict relative risks of toxicities b/w competing plans
- Patients, providers, payors have insight to the anticipated benefits of proton therapy

Comparative Planning: Oropharynx

First 30 Oropharyngeal cancer patients undergoing comparative planning for insurance authorization

- Comparative planning predicted at least 1 clinically relevant reduction in predicted risk of toxicity with proton therapy in all 30 pts
- Most common absolute risk reductions:
- Grade 3+ Mucositis: 86% had >5% reduction in risk
  median 14% reduction in risk
- Grade 2 Trismus: 71% had >10% reduction in risk
  median 10% reduction in risk
- Grade 3+ Aspiration: 64% had >5% reduction in risk
  median 10% reduction in risk
- Grade 3+ Dysphagia: 56% had >5% reduction in risk
  median 11% reduction in risk



Conclusion

The Optimal Environment

- No financial incentives for protons vs IMRT
- Prioritize clinical trials and evidence development
- Try to bring the best treatment to every patient
- Multidisciplinary evaluation and care

Patient Services

- Insurance authorization to advocate for access to care
- Resources for distant patients

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Thank you.