Radiation Oncology for Internists

David J. Sher, MD, MPH
Professor of Radiation Oncology
Medical Director & Vice-Chair of Operations/Quality
University of Texas Southwestern Medical Center

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Disclosures

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- Honorarium from UpToDate, Red Journal
- Employed by UT Southwestern

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Radiation to Most MD's

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Importance

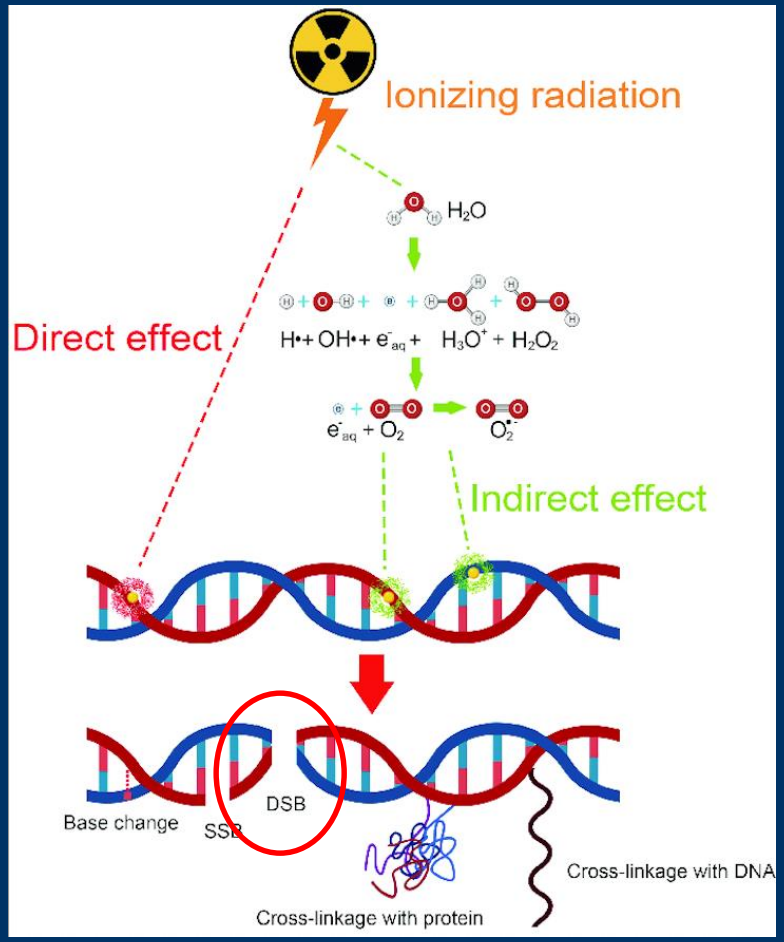
- Radiation therapy is the 2nd most commonly used cancer therapy (behind surgery)
- Radiation therapy is the 2nd most commonly used curative therapy (behind surgery)
- Patients can suffer from acute side effects that may be seen by the internist, but long-term risks are far more likely to present in your practice

What is Radiotherapy?

- High-energy x-rays directed using a variety of techniques to selectively kill cancer cells
  - One chest x-ray: 0.1 mSv
  - One chest CT: 6.1 mSv
  - One fraction of chest radiation: ~ 2 Sv

- The x-ray interacts with the patient and generates high-energy electrons, and those electrons interact with O_2 and H_2O to make free radicals, which cause DNA damage

Schematic



- DS DNA break is the important lesion produced by radiation
- Cell death can occur through mitotic death or apoptosis
- Cell tries to divide, cannot because of damage, and it dies [takes time]

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International Journal of Nanomedicine, Vol 16, 1083-1102

Sparing Normal Tissue?

- Two fundamental mechanisms

- Biological
  - Cancer cells are not good at repairing the damage
    - Defective DNA damage repair
  - Normal cells have conserved mechanisms to heal
    - Different tissues have different abilities to heal

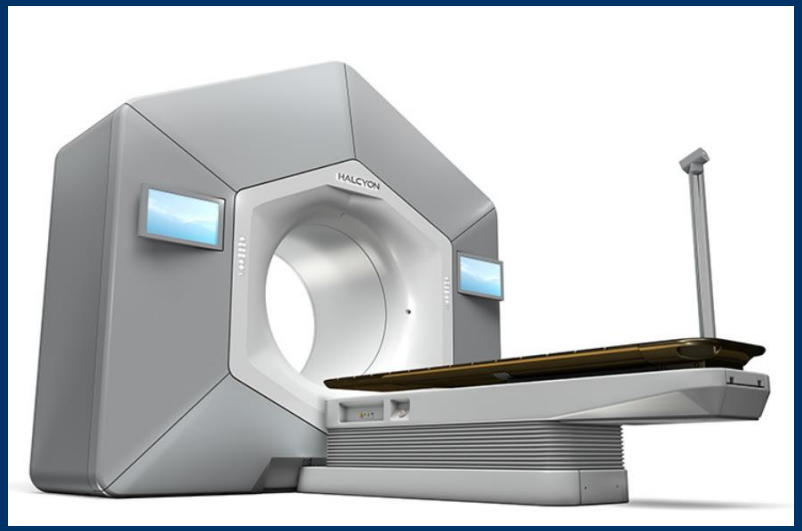
- Technological
  - We have gotten very good at increasing the accuracy of the beam

How Is Radiation Made

- The vast majority of radiotherapy is delivered on a linear accelerator

- Electrons are accelerated to very high energies (MeV) and then hit a tungsten target, and that interaction generates photons, which are directed to the patient

Linear Accelerator



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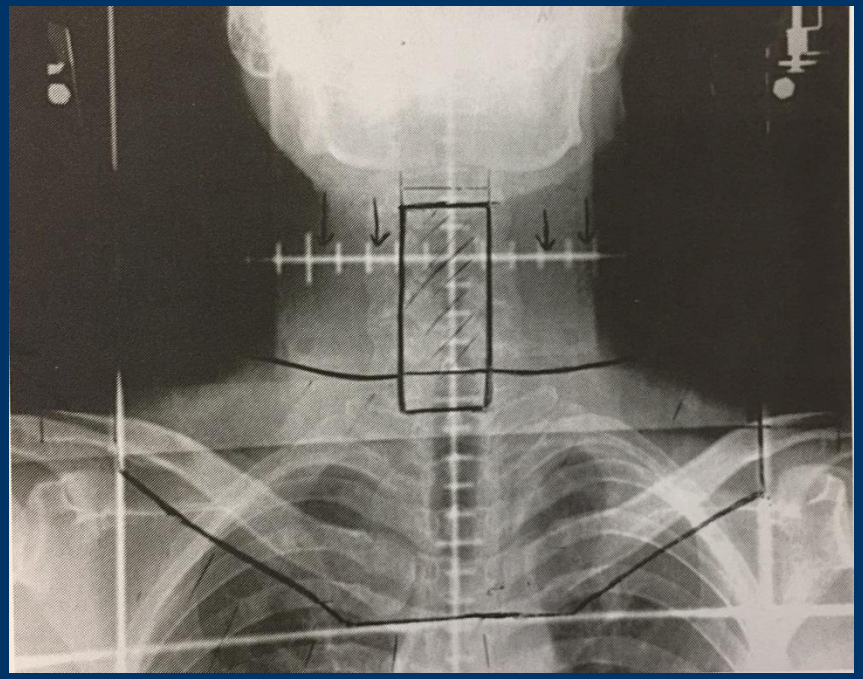
Radiation Technologies

- 2D (until 1990's)
- 3D (1990's and 2000's)
- IMRT/VMAT (2000's through today)
- Proton therapy (2000's through today)
- Adaptive radiotherapy (2020's through today)

2D Radiotherapy



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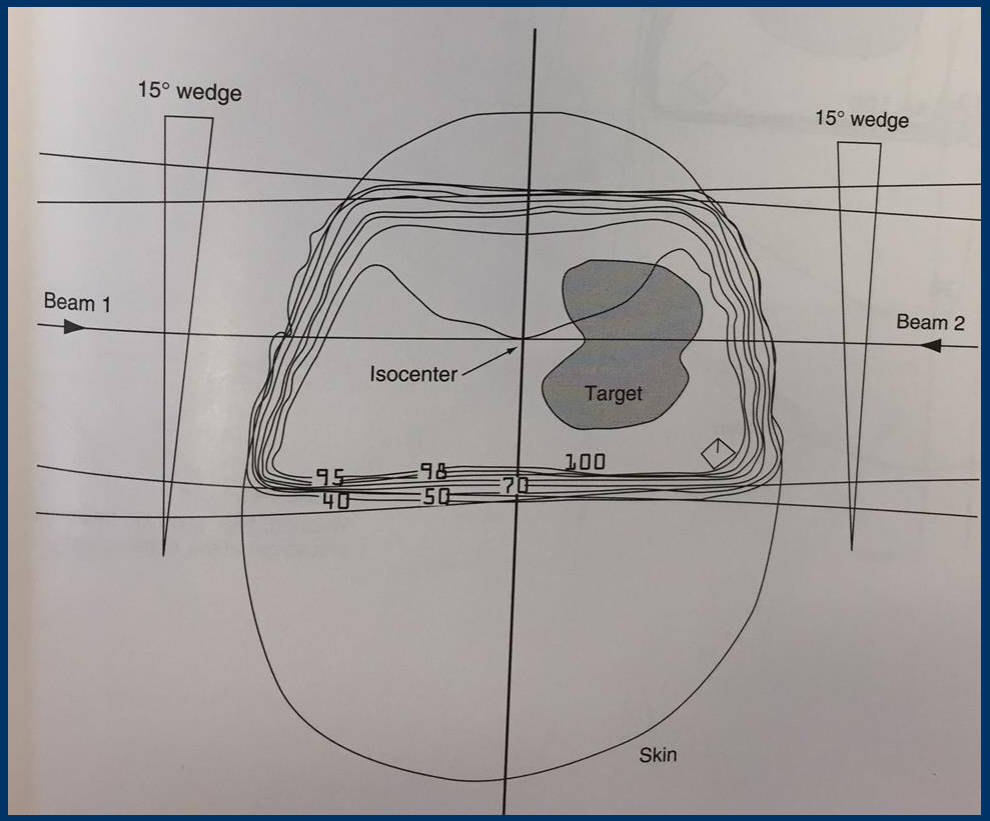
2D Planning



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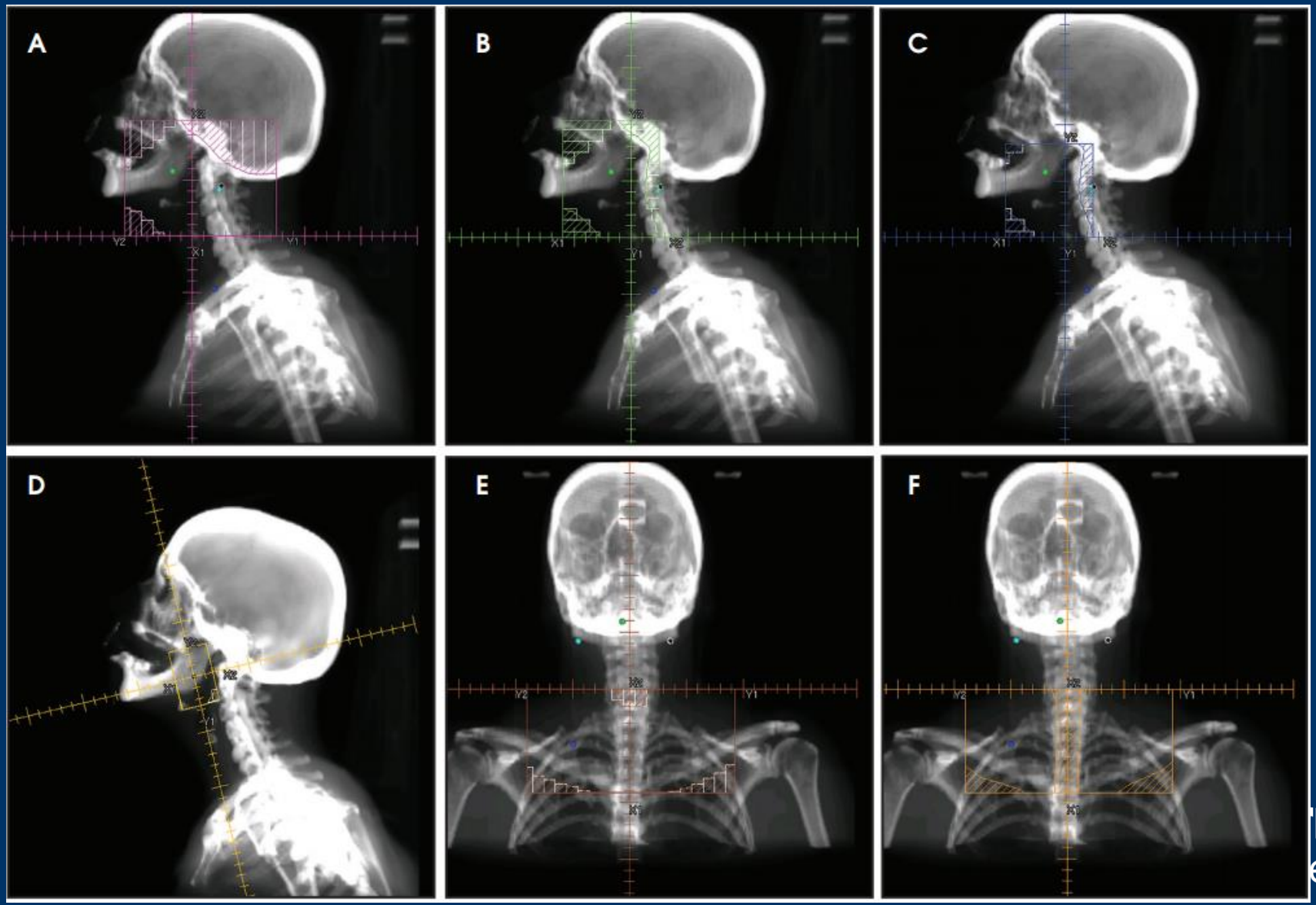
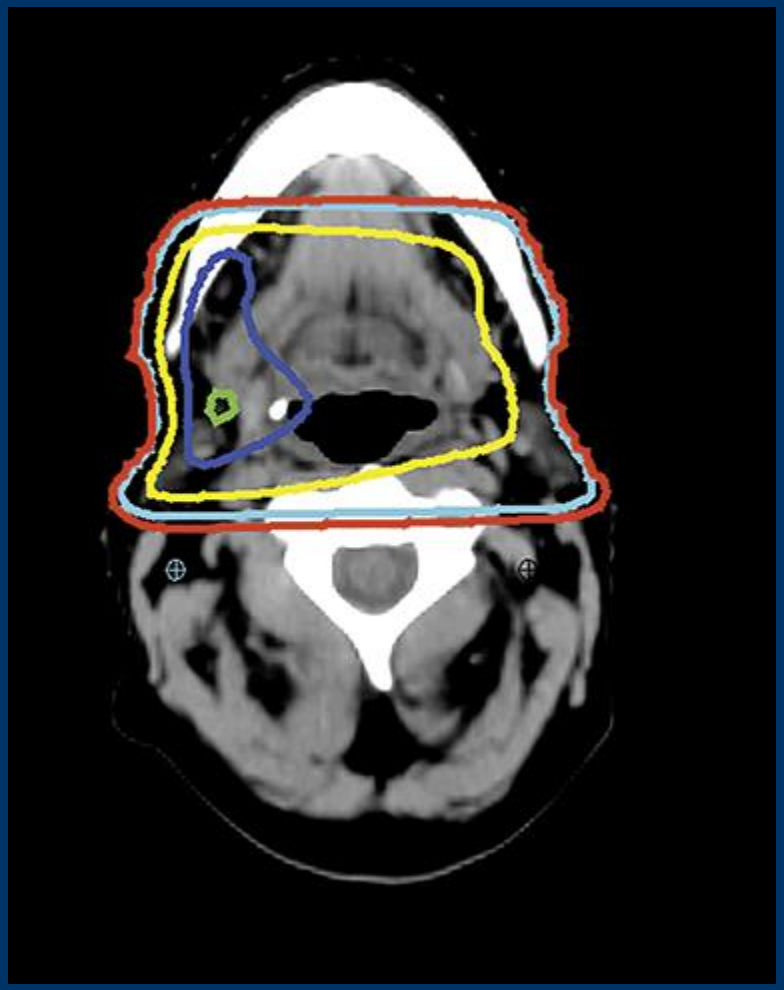
3D Fields



3D Planning



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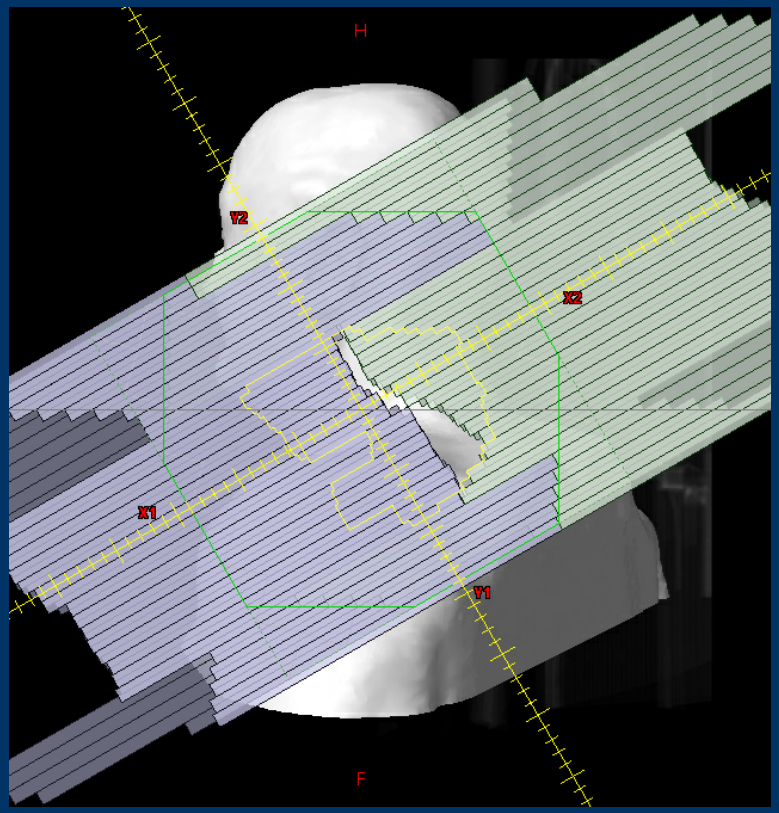
IMRT

- Intensity modulated radiation therapy
  - Arc version: volumetric modulated arc therapy (VMAT)
- Two characteristics:
  - Inverse planning
  - Intensity modulation



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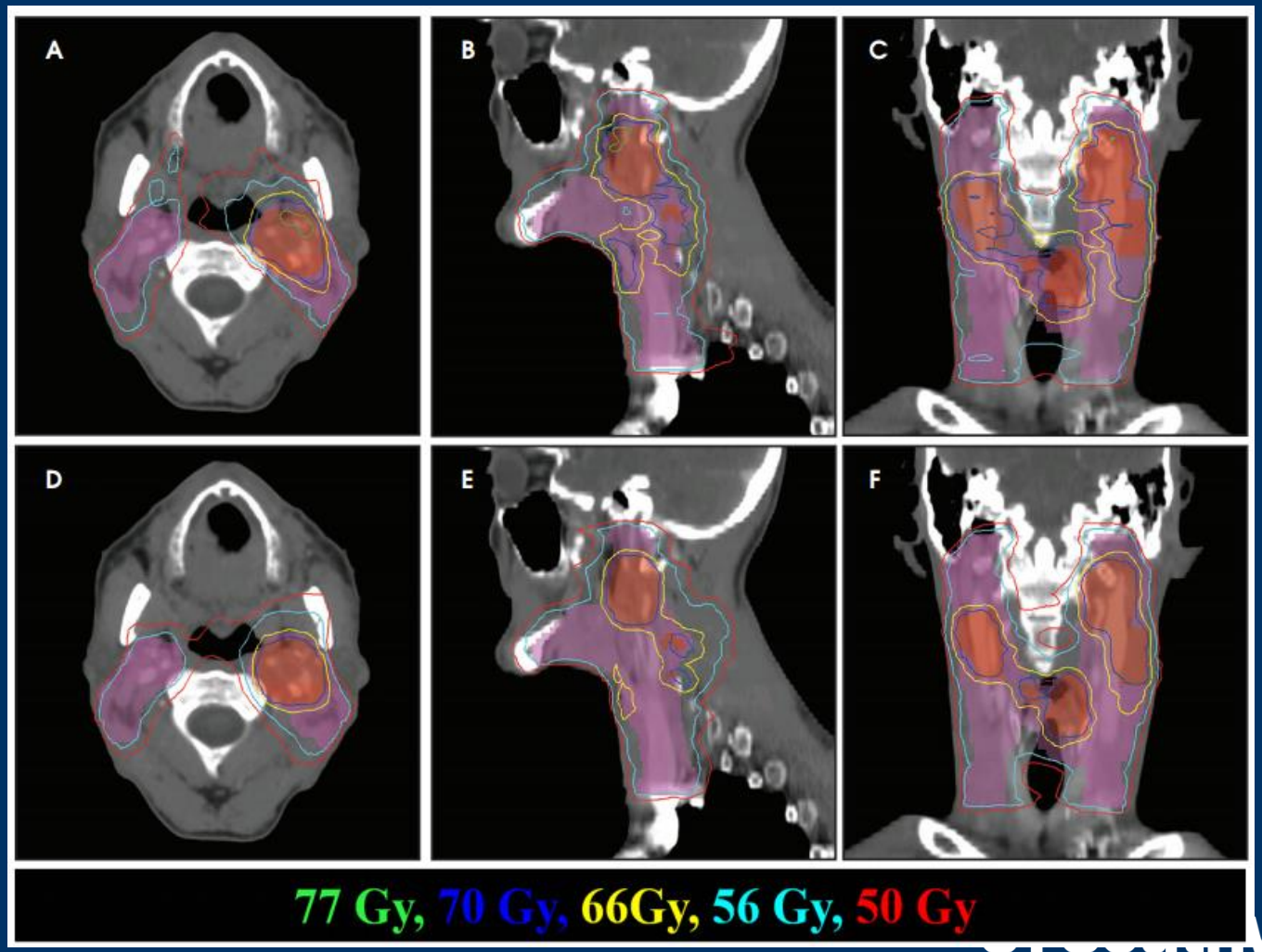
Now, Plans Look Like



Fractionation

- Historically, radiation therapy was delivered daily, 5 days per week, for 5-8 weeks
- Canon was that lower doses per day spread out over many weeks led to fewer side effects and superior outcomes
  - Helps that in the US we are paid by the fraction…
- Technology and prospective study have shown that shorter fractionation courses are the future

Hypofractionation

- Many disease sites have progressively reduced the number of fractions by increasing the dose per fraction (hypofractionation)

- Phase III randomized trials in breast, prostate, GBM, rectal cancer, have shown equivalent cancer control, toxicity and survival outcomes in 5-15 fractions

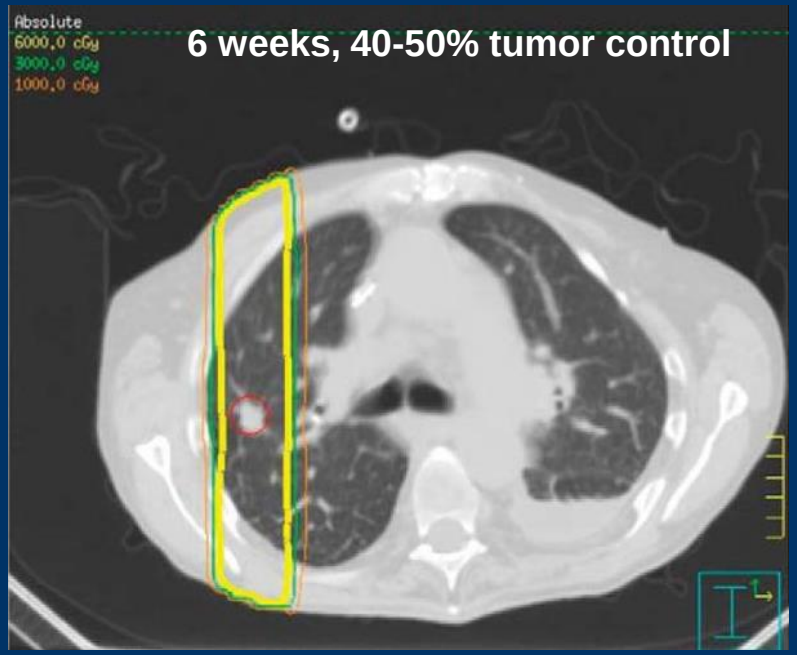
Standard Regimens at UTSW

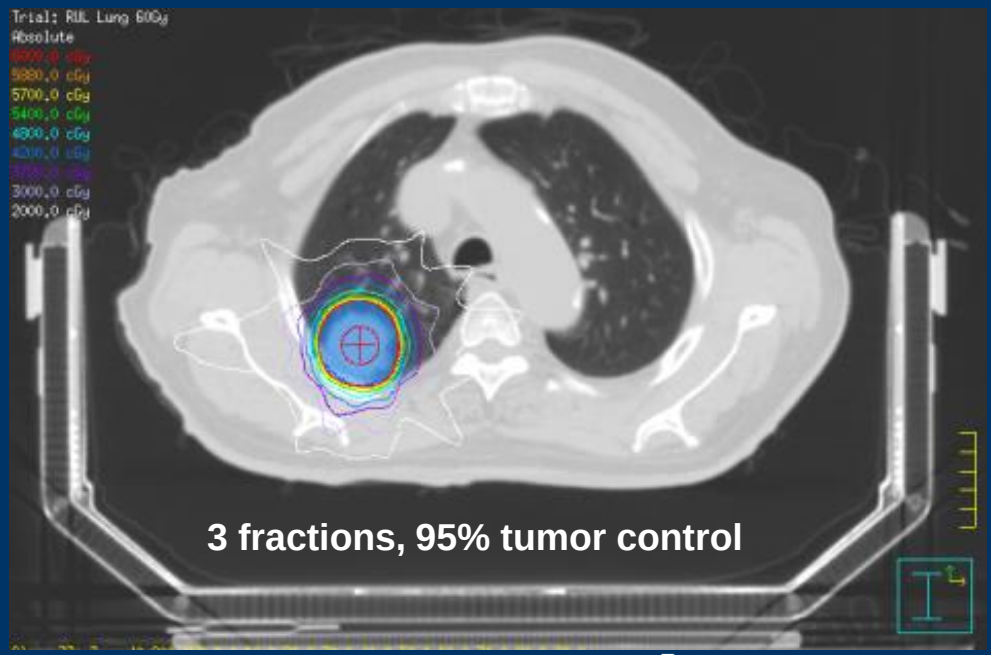
- We average only 12 fractions per patient (all comers)

- Based on high-level randomized data:
  - Breast: 5 to 20 fractions
  - Prostate: 5 to 20 fractions
  - Rectal: 5 fractions
  - Pancreas: 5 fractions
  - Most brain: 1-5 fractions

Stereotactic Radiotherapy

- **Stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SAbR) have revolutionized radiotherapy**





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SBRT Sites (5 fractions or less)

- Lung
- Brain
- Prostate
- Pancreas
- Breast
- Head and neck (larynx)
- Kidney

Great! What Can Go Wrong?

- Radiotherapy leads to a variety of acute and chronic complications

- Acute (typically managed by rad onc)
  - Dermatitis (cellulitis is quite rare)
  - Alopecia
  - Fatigue
  - Mucositis/esophagitis (thrush is common)
  - Enteritis/proctitis/cystitis

Late Side Effects

- Late side effects are the key complications which may present to internists and require their expertise

- Cardiovascular
  - Cardiac
  - Cerebrovascular

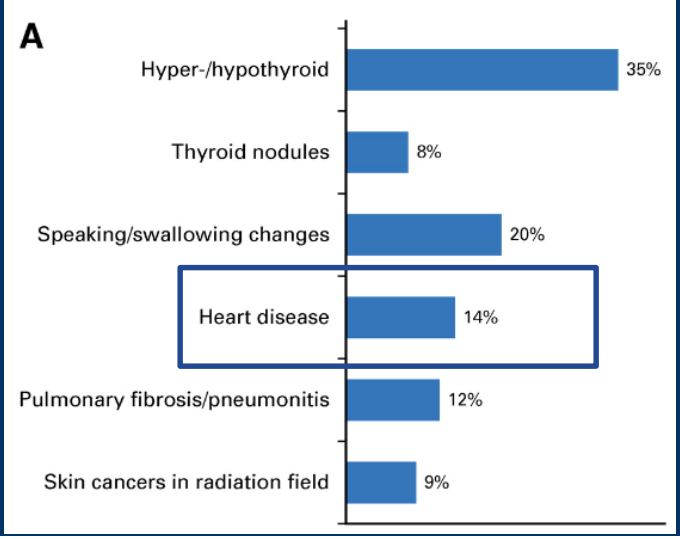
- Second malignancies

Late Toxicity Burden

- Lymphoma studies often show the best data because of long follow-up and fewer competing risks

- Recent study of 1,000 lymphoma survivors (Frick et al, JCO Clin Cancer Informatics 2018) showed the burden was across the body and increased over time

Late Toxicity Burden



Effect	Time in Follow-Up, Years				Odds Ratio (per decade in follow-up)	*P*
	< 2	2-5	5-9	≥ 10		
Radiation related						
Hyper-/hypothyroid	0	20	42	61	3.06	< .01
Thyroid nodules	0	5	8	15	2.16	< .01
Speaking/swallowing changes	9	20	17	28	2.08	< .01
Heart disease	0	5	4	31	2.80	< .01
Pulmonary fibrosis/pneumonitis	5	20	13	19	1.44	.117
Skin cancers in radiation field	0	0	13	20	2.50	< .01
Secondary breast cancer						

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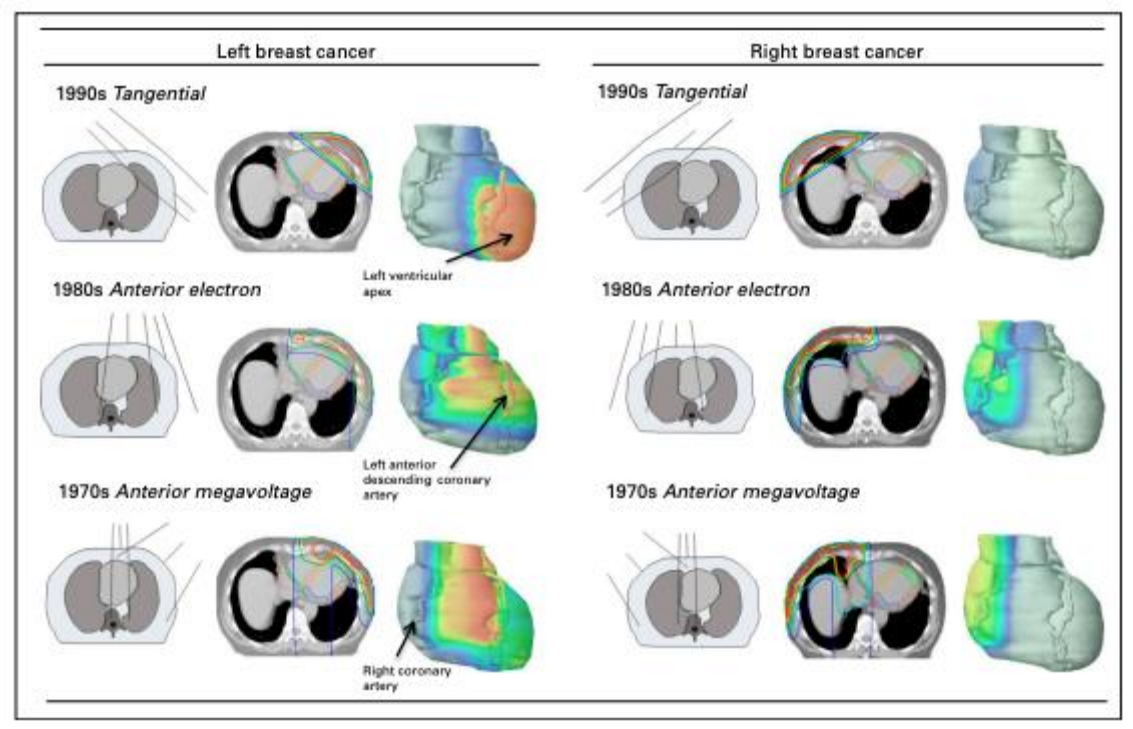
Breast Cancer

- **Traditional left-sided breast cancer fields included the left ventricle and LAD**



Taylor et al, JCO 2018

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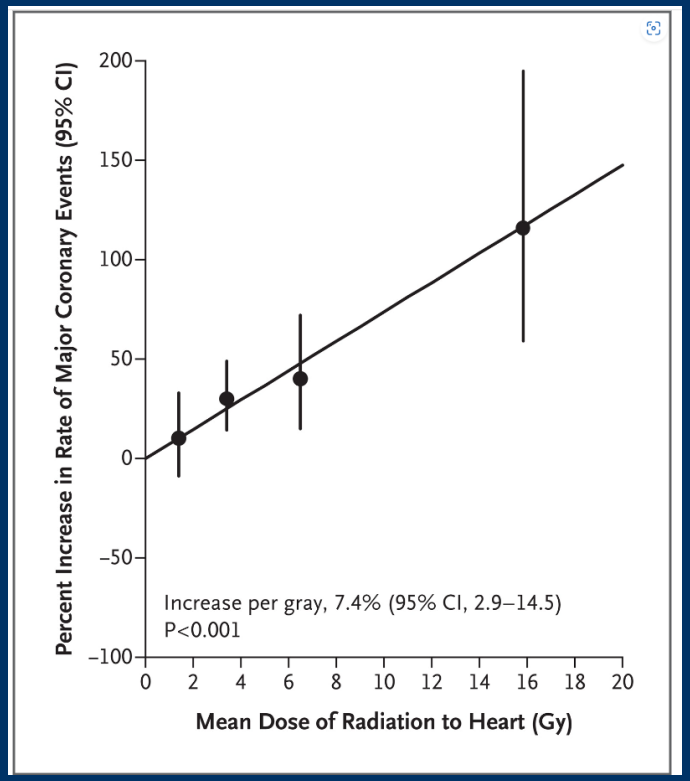
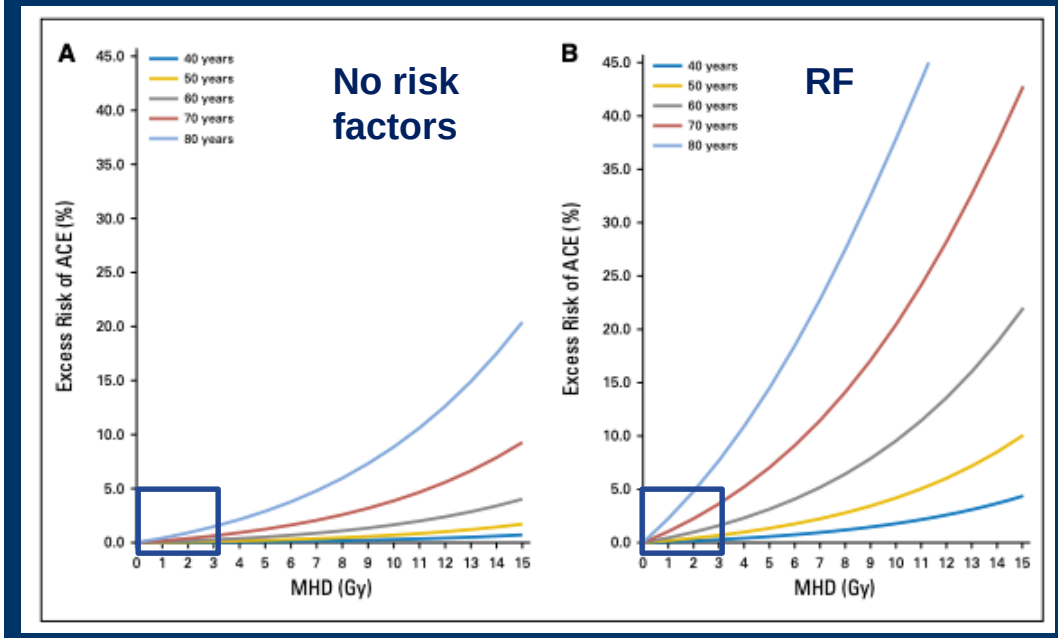
Real-World Data

- Darby (NEJM 2013)



- Van den Boggard (JCO 2017)



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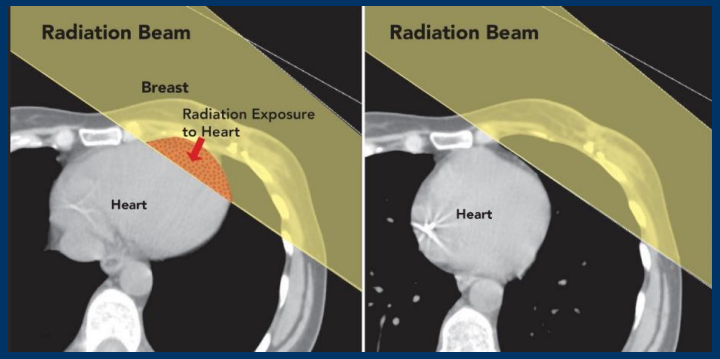
Solutions

- Breath-hold systems
- Prone treatment
- IMRT
- Partial breast irradiation
- Adaptive radiation



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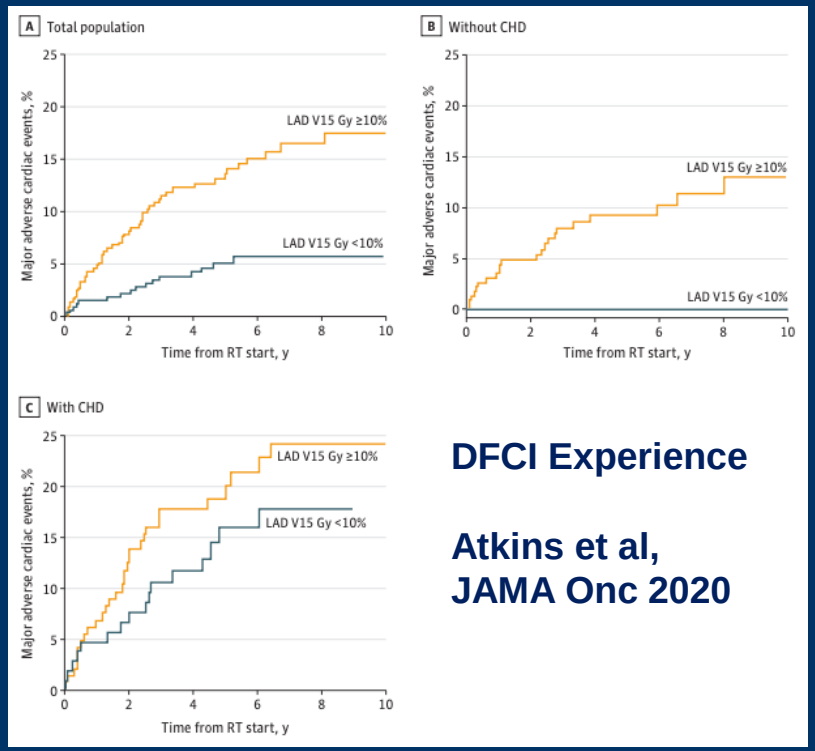
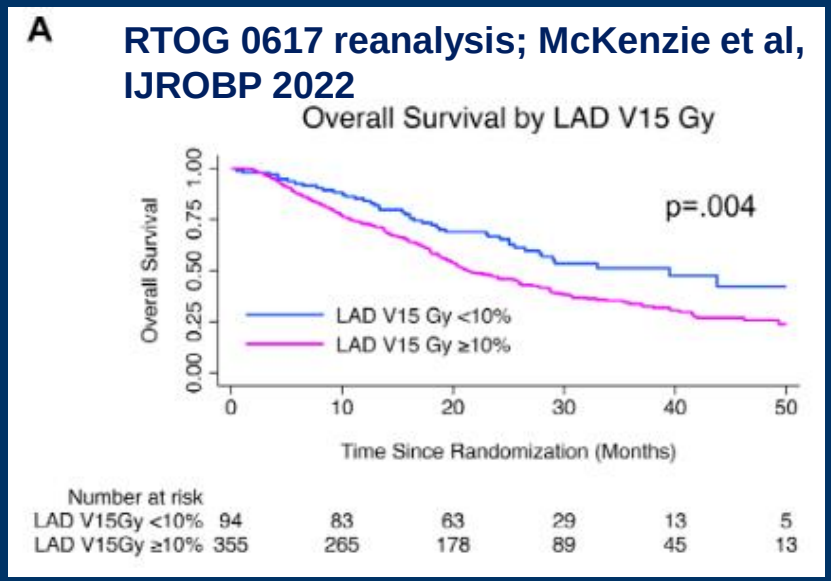
Lung Cancer

- **Many competing risks for non-cancer mortality, but heart dose (likely LAD) is predictive of major cardiac events**



DFCI Experience

Atkins et al, JAMA Onc 2020



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Carotid Stenosis/Stroke

- **Large database analyses have suggested a slight but significant risk of stroke after RT**

- **Netherlands Cancer Institute (Dorresteijn JCO 2001)**
  - **Cumulative incidence @ 15 years: 12.0%**
  - **Median interval to stroke 10.9 years**

Table 6. RR and AER of Stroke According to Follow-Up Interval, Age at RT, and Sex

	Person-Years	Observed Cases	Expected Cases	RR	95% CI	AER/1,000 Patients/yr*
Follow-up time						
0-9 years	2,313	6	1.63	3.7	1.3-8.0	1.9
> 10 years	514	8	0.79	10.1	4.4-20.0	14.0
Age at RT						
< 50 years	1,659	5	0.51	9.8	3.2-22.9	2.7
> 50 years	1,351	9	1.99	4.5	2.1-8.6	5.2
Sex						
Male	1,755	8	1.91	4.2	1.8-8.2	3.5
Female	1,256	6	0.59	10.2	3.7-22.2	4.3

Carotid Stenosis/Stroke

- Duke developed a protocol to survey patients with annual carotid U/S (Dorth, Head Neck 2013)
- 224 patients in total
  - 35 developed stenosis
  - 9/18 with high-grade underwent surgery
  - 2 experienced stroke

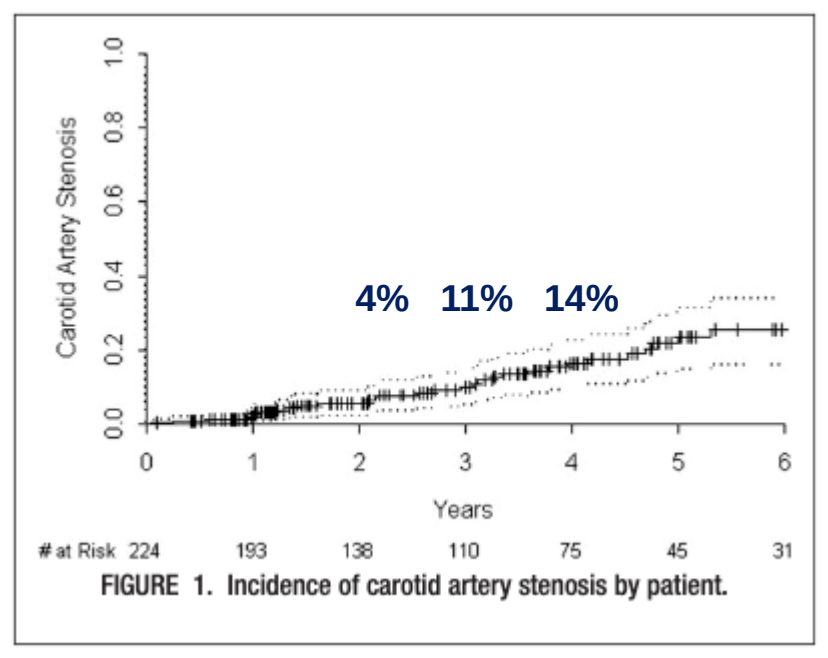

FIGURE 1. Incidence of carotid artery stenosis by patient.

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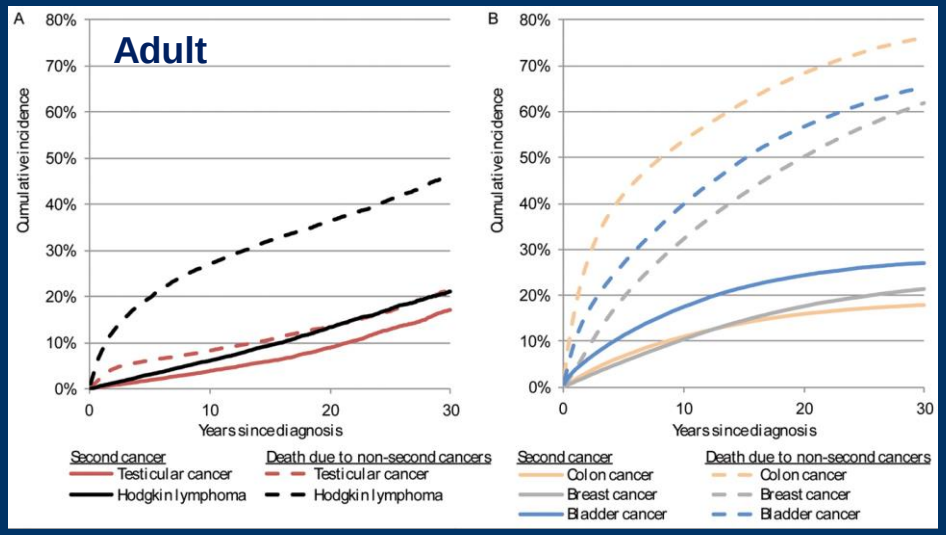
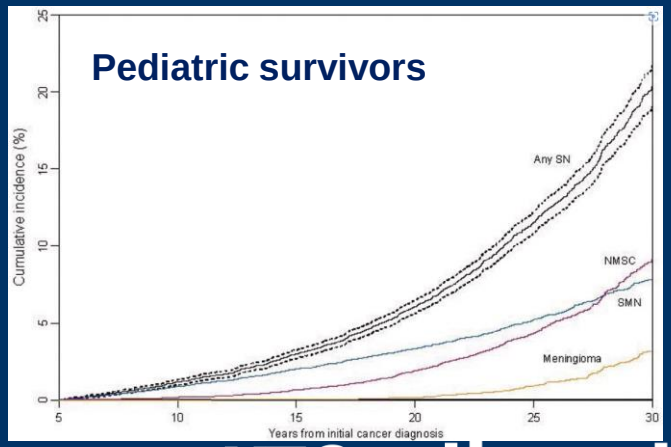
Second Malignancies

- Secondary cancers induced by radiotherapy are the most concerning/scary aspect of RT
- All patients are at risk for 2nd malignancies due to genetics, behavior, chemo and radiation





Morton et al, ASCO Educational Book 2018

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Risk Factors

- **Despite fear of radiation-induced malignancies, estimated that only 10% of all secondary malignancies are attributable to RT (de Gonzalez, Lancet Oncol 2011)**

	Number of second solid cancers in patients treated with radiotherapy*	Number of patients	Excess cancers (95% CI)†	Attributable risk (95% CI)
Oral/pharynx	3683	24 880	182 (53 to 310)	5% (1 to 8)
Salivary gland‡	309	3007	37 (1 to 71)	12% (0 to 23)
Rectum‡	1568	21 841	112 (41 to 184)	7% (3 to 12)
Anus	323	3444	32 (−14 to 74)	10% (−4 to 23)
Larynx	3583	17 070	193 (32 to 350)	5% (1 to 10)
Lung (non-small cell)	2395	51 270	152 (82 to 223)	6% (3 to 9)
Soft tissue (non-limbs)	120	1602	18 (−2 to 39)	15% (−2 to 32)
Female breast	12 450	150 661	660 (454 to 866)	5% (4 to 7)
Cervix‡	1289	14 685	214 (130 to 295)	17% (10 to 23)
Endometrium‡	3269	29 338	286 (165 to 407)	9% (5 to 12)
Prostate‡	11 292	128 582	1131 (956 to 1307)	10% (8 to 12)
Testes (seminomas)	628	7862	150 (56 to 233)	24% (9 to 37)
Eye and orbit	112	1085	4 (−12 to 22)	4% (−11 to 20)
Brain/CNS	314	13 220	28 (−11 to 66)	9% (−3 to 21)
Thyroid‡	959	16 934	67 (6 to 128)	7% (1 to 13)
Total	42 294	485 481	3266 (2862 to 3670)	8% (7 to 9)

*In all patients (defined as ≥1 year survivors). †Estimated in 5 year or longer survivors calculated with the results from the Poisson regression model (figure 1). ‡Second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).

Table 4: **Estimated number of excess second solid cancers related to radiotherapy treatment and attributable risk in those treated with radiotherapy by first cancer site**

	Latency 5–9 years	Latency 10–14 years	Latency ≥15 years	p-trend
Oral/pharynx	1·12 (0·99 to 1·27)	1·14 (0·95 to 1·38)	0·95 (0·74 to 1·22)	0·34
Rectum*	1·13 (0·94 to 1·35)	1·33 (1·03 to 1·70)	0·91 (0·64 to 1·27)	0·54
Larynx	1·57 (1·08 to 2·36)	1·04 (0·66 to 1·70)	1·29 (0·75 to 2·30)	0·45
Lung (non-small cell)	1·12 (0·98 to 1·27)	1·37 (1·12 to 1·65)	1·62 (1·23 to 2·09)	0·0079
Female breast	1·17 (1·05 to 1·30)	1·42 (1·24 to 1·62)	1·56 (1·34 to 1·81)	0·0013
Cervix (external beam)*	1·18 (0·79 to 1·75)	1·55 (1·00 to 2·40)	2·59 (1·84 to 3·68)	0·0032
Endometrium (external beam)*	1·30 (1·08 to 1·56)	1·99 (1·60 to 2·47)	2·18 (1·78 to 2·65)	<0·0001
Prostate (external beam)*	1·39 (1·29 to 1·50)	1·59 (1·41 to 1·80)	1·91 (1·53 to 2·38)	0·0031
Thyroid*	0·89 (0·49 to 1·55)	1·03 (0·47 to 2·14)	1·21 (0·64 to 2·17)	0·47

Data are relative risk (RR; 95% CI) unless otherwise stated. RR adjusted for sex, attained age, and attained year through the use of external rates and additionally adjusted for stage, age at diagnosis, and year of diagnosis through stratification. For endometrial and prostate cancer the group treated with external beam radiotherapy includes patients treated with external beam and brachytherapy. *Second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).

Table 3: **Relative risk of second solid cancer at high-dose sites for radiotherapy versus no radiotherapy by time since first cancer diagnosis (latency) and first cancer site**

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What To Do?

- **Mitigate modifiable risk factors**
  - **Smoking, smoking, smoking**
  - **Alcohol use**
  - **Obesity**

- **Be vigilant**
  - **From an internal medicine perspective, no defined protocol for long-term toxicity surveillance**
  - **Quick referral to cardiology/cardio-oncology**
  - **Err on the side of screening (much research needs to be done)**

CNS / Head and Neck

- Dental decay and osteonecrosis
- Dysphagia
  - Can lead to life-threatening aspiration
- Hypothyroidism
- Memory loss (short-term)

Thoracic and Breast

- Cardiac (as mentioned)
- Pneumonitis
  - Typically 1-3 months after radiation is over
  - Very different treatment than pneumonia
- Esophagitis (lung)
- Fat necrosis/fibrosis (breast)

Abdomen/Pelvis

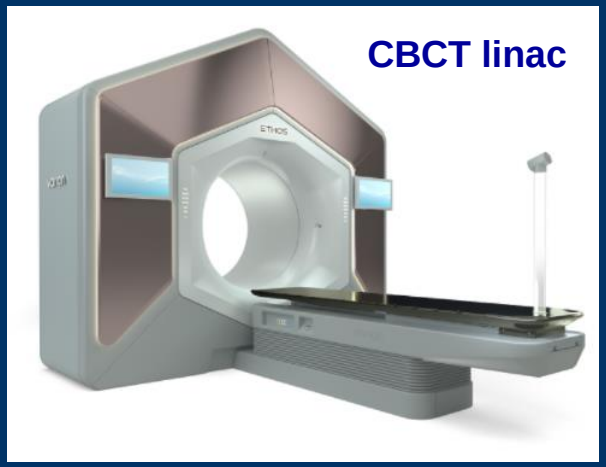
- Chronic enteritis
- Proctopathy
- Cystitis and urethritis
- Sexual dysfunction (very important!)
  - Sexuality issues
  - Potency
  - Vaginal stensosis/dryness

The Field is Advancing: FAST

- **Proton radiotherapy**
  - **Best suited for pediatric/young adult populations**
  - **Paucity of data it is superior in other conditions**

- **Adaptive radiotherapy**
  - **MRI, CT and PET-CT scans can now be used to *guide* radiotherapy and *change* the treatment on any given day**
  - **Provides incredible power to adapt the radiation plan to the patient's individual anatomy and biology**

Adaptive Machines



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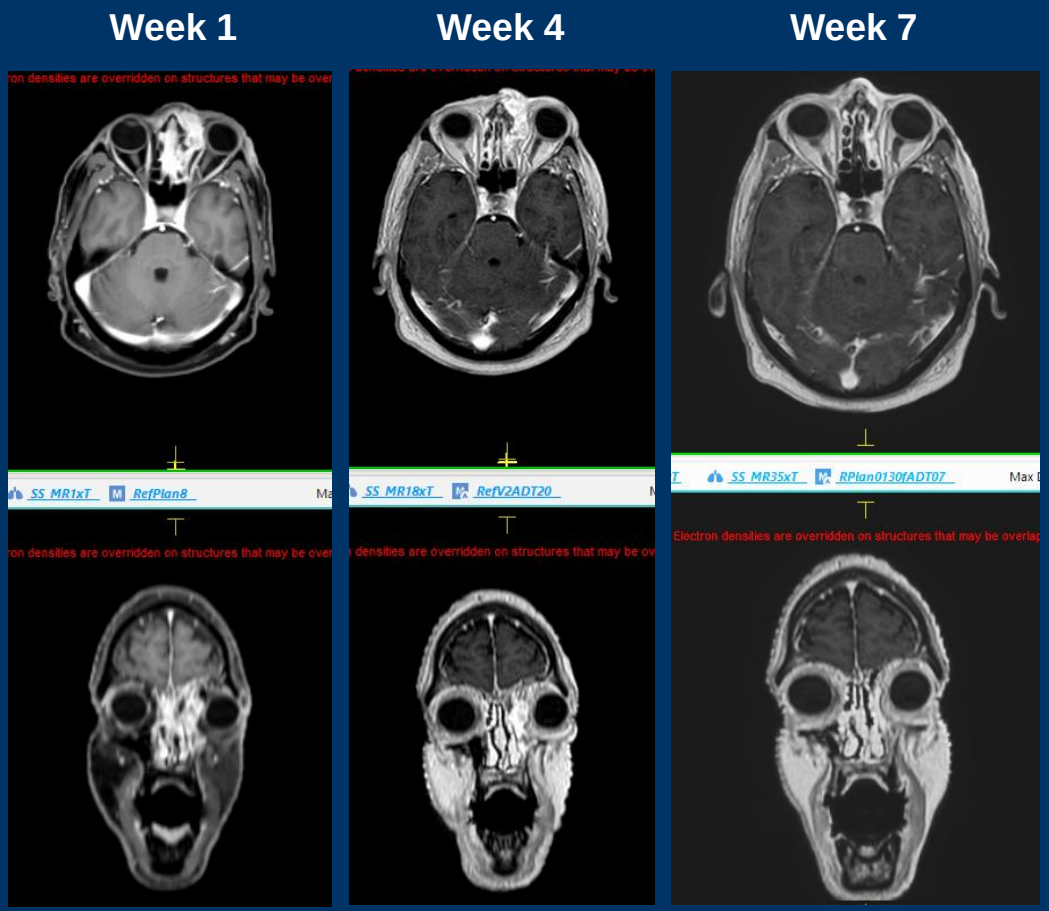
Adaptation is Powerful

- Disease dramatically reduced in size over treatment
- Reduced treatment volumes 4 times using these images from the machine



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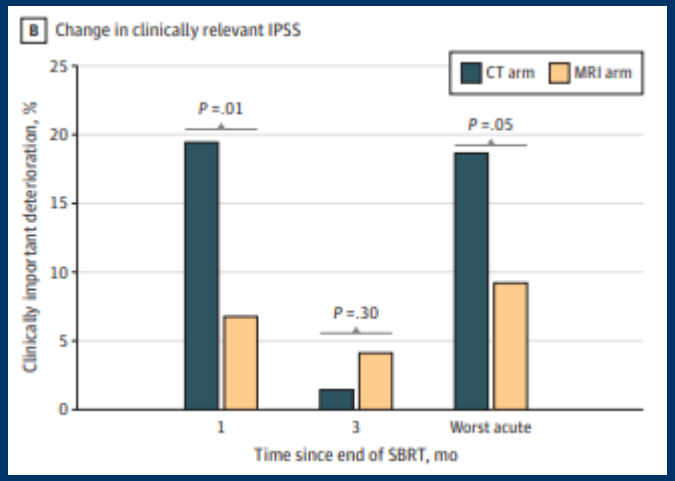
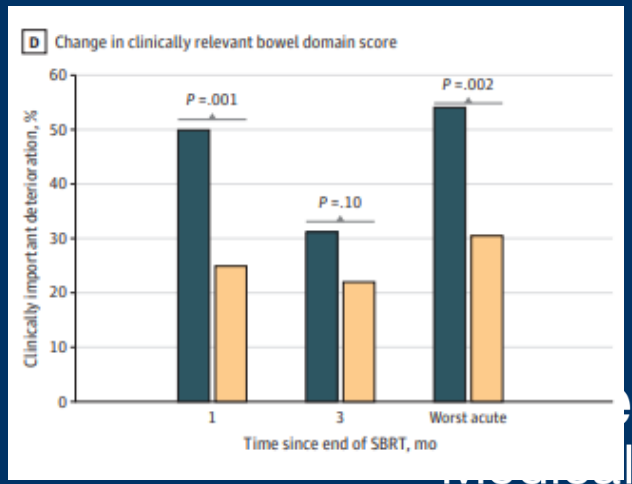
Example of Adaptive RT

- **MIRAGE was a RCT of prostate SBRT using standard treatment or MRI-based treatment with tighter margins (JAMA Onc 2023)**

- **Significant improvement in acute toxicity**



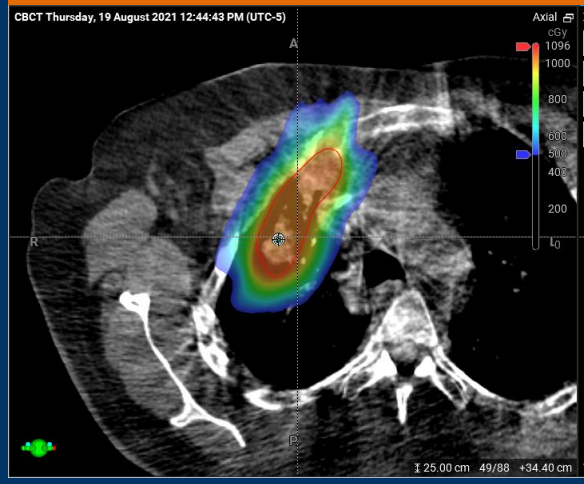


The Future

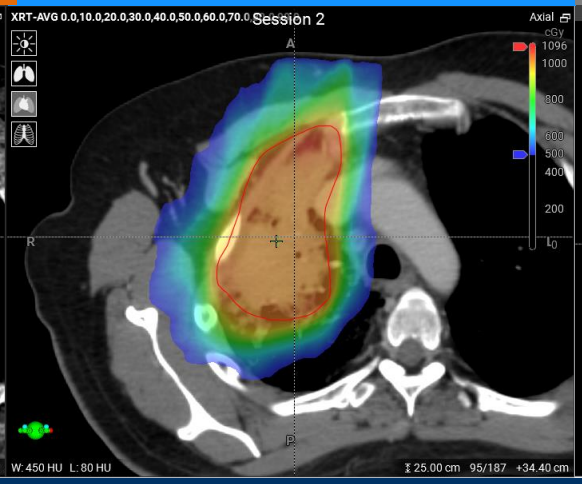
- **Incorporating pre- and on-treatment clinical, radiologic/radiomic, and biological data to fully personalize each patient's radiotherapy**
- **PULSAR: Personalized Ultra-Fractionated Stereotactic Adaptive Radiotherapy**
- **Spread out radiation doses (pulses) to adapt each dose to the patient's disease**

Example

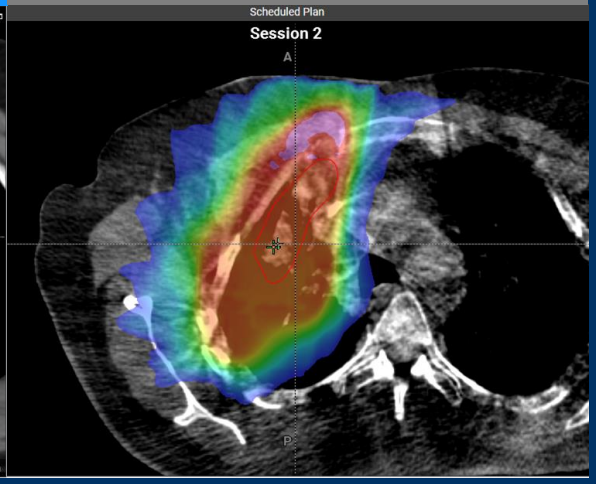
2nd Pulse –Adapted Plan (08/19/2021)



Preplan (07/22/2021)



2nd Pulse –Scheduled Plan (08/19/2021)



Courtesy Robert Timmerman, MD

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Conclusions

- Radiotherapy has been and will be a fundamental component of cancer treatment
- Advances in treatment have dramatically improved control and toxicity, but…
- Complications may last a lifetime, and cognizance is important for recognition
- Future of adaptation is bright

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Questions?

- **Please contact me!**
- **david.sher@utsw.edu**
- **@davidshermd**

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