Stereotactic Ablative Radiotherapy for Prostate Cancer

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Scope of the Problem

Estimated New Cases

Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All sites	856,370	100%	All sites	878,980	100%

Estimated Deaths

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	323,630	100%	All sites	286,010	100%

Incidence Trends

- An estimated 164,690 new cases of prostate cancer will be diagnosed in the US during 2018
- In the late 1980s and early 1990s, incidence rates for prostate cancer spiked dramatically, (widespread screening with the PSA blood test)

Incidence Trends

- Decline in rates since around 2000
- Likely due to recommendations against routine PSA screening beginning in 2008
- From 2010 to 2014, the rate decreased by about 10% per year

Mortality Trends

- An estimated 29,430 deaths from prostate cancer will occur in 2018
- Prostate cancer death rates have been decreasing since the early 1990s, although rates appear to have stabilized from 2013 to 2015

Risk Groups

Risk group	Clinical/pathologic features
Very low[g]	• T1c AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[h] AND • PSA density <0.15 ng/mL/g
Low[g]	• T1-T2a AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL
Favorable intermediate[g]	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 OR • PSA 10–20 ng/mL AND • Percentage of positive biopsy cores <50%
Unfavorable intermediate[g]	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR • PSA 10–20 ng/mL
High	• T3a OR • Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 OR • PSA >20 ng/mL
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Gleason score 8–10/ grade group 4 or 5

Treatment of Localized Disease

- Surgery
- Radiotherapy (RT)
- Active surveillance (low risk only)
- No difference in risk of dying of prostate cancer 10 years after diagnosis between these options
  - Surgery and RT associated with lower risk of disease progression and metastasis

N Engl J Med. 2016 Oct 13;375(15):1415-1424. doi: 10.1056/NEJMoa1606220. Epub 2016 Sep 14

Patient Reported Outcomes

- 1643 men in the Prostate Testing for Cancer and Treatment (ProtecT) trial
- Questionnaires before diagnosis, at 6 and 12 months after treatment, and annually thereafter
  - urinary, bowel, and sexual function
  - quality of life
  - anxiety and depression
  - general health

N Engl J Med. 2016 Oct 13;375(15):1425-1437. doi: 10.1056/NEJMoa1606221. Epub 2016 Sep 14.

Patient Reported Outcomes

- Prostatectomy had the greatest negative effect on sexual function and urinary continence
  - Although there was some recovery, these outcomes remained worse in the prostatectomy group than in the other groups throughout the trial
- The negative effect of radiotherapy on sexual function was greatest at 6 months
  - sexual function then recovered somewhat and was stable thereafter
  - radiotherapy had little effect on urinary continence

N Engl J Med. 2016 Oct 13;375(15):1425-1437. doi: 10.1056/NEJMoa1606221. Epub 2016 Sep 14.

Patient Reported Outcomes

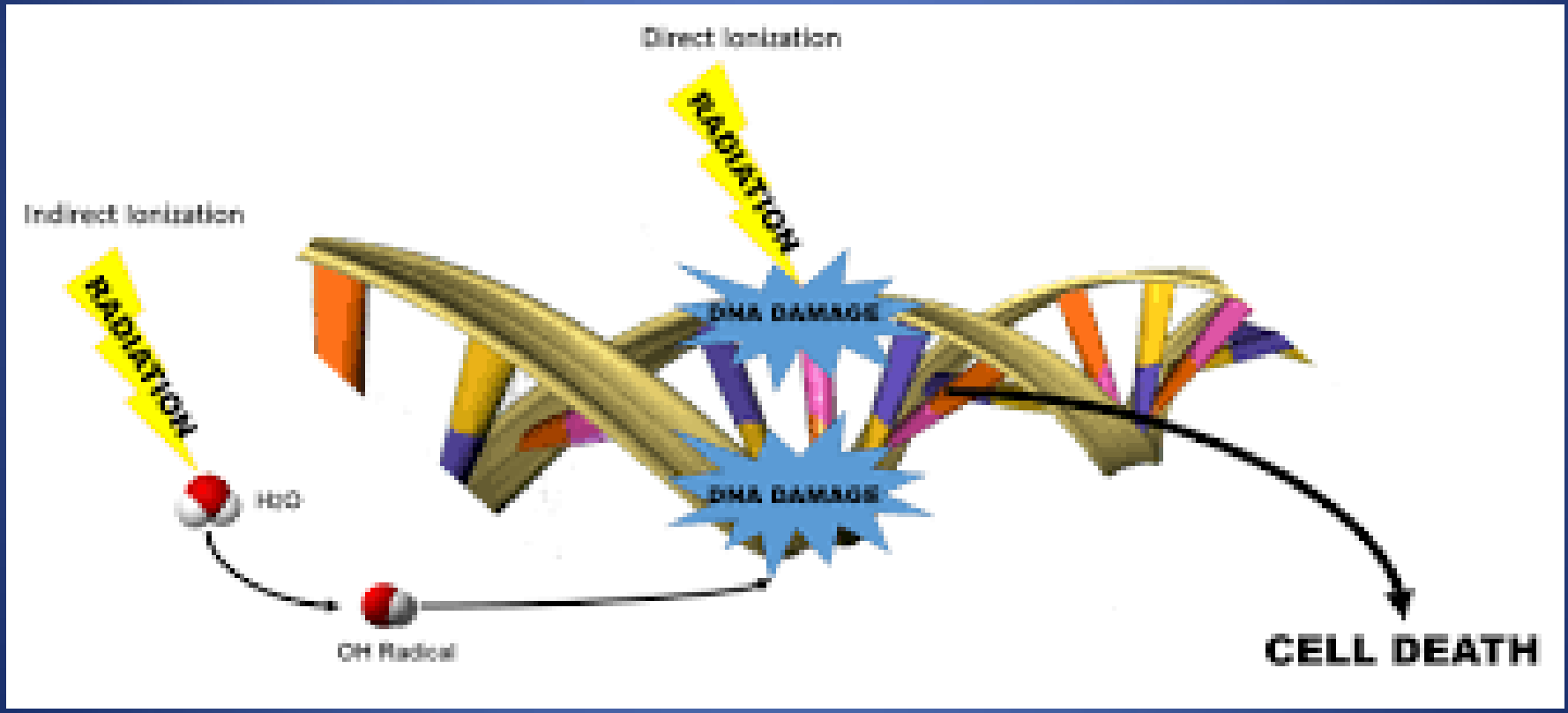
- Sexual and urinary function declined gradually in the active-monitoring group
- Bowel function was worse in the radiotherapy group at 6 months than in the other groups but then recovered
- Urinary symptoms were worse in the radiotherapy group at 6 months but then mostly recovered and were similar to the other groups after 12 months
- No significant differences were observed among the groups in measures of anxiety, depression, or general health-related or cancer-related quality of life

N Engl J Med. 2016 Oct 13;375(15):1425-1437. doi: 10.1056/NEJMoa1606221. Epub 2016 Sep 14.

Radiotherapy 101

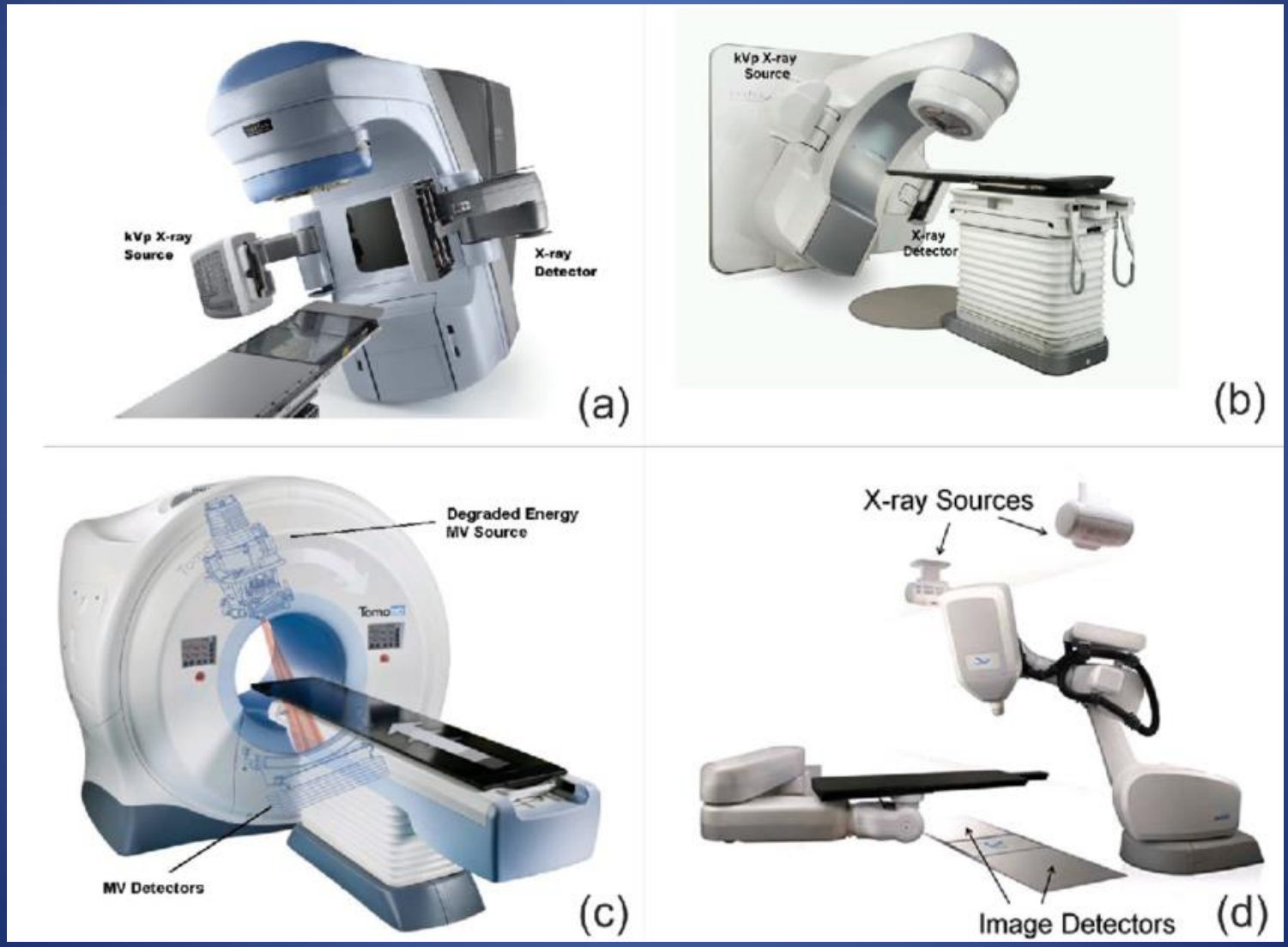
- Radiotherapy uses a focused beam of energy to damage cancerous cells while minimizing exposure to healthy tissue
- Radiation damages the DNA in cancer cells, which interrupts their ability to reproduce, causing them to die
- Normal cells can recover from radiation more easily
- Treatment is delivered to the target site with a machine called a linear accelerator (linac)

How Radiotherapy Works



Linear Accelerator

Types of Linacs



Radiosurgery

- Radiosurgery is a non-invasive treatment technique used primarily to ablate tumors
- Most suitable for small, well-defined tumors
- Despite the use of the word "surgery" in its name, radiosurgery does not involve removing the tumor
- Instead, a focused high-intensity beam of radiation is used to target a tumor while minimizing dosage to healthy tissue
- Highly precise, intensified form of radiotherapy

Radiosurgery

- Traditional radiotherapy can include up to 40 treatments (5 days a week for several weeks)
- Radiosurgery is performed in five sessions or less over a period of two weeks.
- Although the total number of radiosurgery treatments is fewer, each session usually takes more time in order to make sure the patient is accurately positioned
- Stabilization devices are often used to ensure proper positioning

Treatment Techniques

- Stereotactic radiosurgery (SRS) refers to the treatment of tumors in the brain or spinal column
- Stereotactic body radiation therapy (SBRT) is a very similar technique to SRS but is used for targets that are outside the brain (lung, prostate, liver, pancreas)
- The latest term for these treatments is stereotactic ablative radiotherapy (SABR)

Technology

- Intensity modulated radiation therapy (IMRT) uses 3-D scans of your body to guide the beams of radiation to the tumor from many different angles
- At each of these angles, the intensity of the radiation is varied (modulated) and the shape of the beam is changed to match the shape of the tumor
- These adjustments enable the prescribed amount of radiation to be delivered to each part of the tumor, while minimizing exposure to the surrounding healthy tissue

Technology

- Image-guided radiation therapy (IGRT) is a technique that uses 2D and 3D scans of the patient to guide the beams of radiation to the tumor from many different angles
- Before each treatment, a CT scan is taken in order to accurately capture the position of the tumor that day
- Final adjustments are then made to position the patient for accuracies of less then half of a millimeter.

VMAT

- Volumetric Arc Therapy (VMAT) is an advanced form of radiotherapy
- Unlike older IMRT treatments, during which the machine must make repeated stops and starts to treat the tumor from a number of different angles, VMAT can deliver the dose to the entire tumor in a 360-degree rotation, typically in less than two minutes
- Up to eight times faster than what was previously possible

SABR for Early Prostate Cancer

- 5 treatments (delivered every other weekday)
- Theoretical advantage to delivering a higher daily dose over a shorter amount of time
- 8 studies published to date (over 2000 patients)
- Primarily used in low-risk patients
- Serious side effects seen in less than 5%

Anticancer Res. 2018 Mar;38(3):1231-1240

SABR for Early Prostate Cancer

SABR for Early Prostate Cancer

- PSA control approaches 100% for low-risk patients and is over 90% for intermediate-risk
- This compares very favorably with longer treatment regimens
- As of 2018, SABR now recommended as an option by the NCCN for patients with low-risk disease

Cancer Treat Rev. 2016 Jul;48:50-60. doi: 10.1016/j.ctrv.2016.06.006. Epub 2016 Jun 17

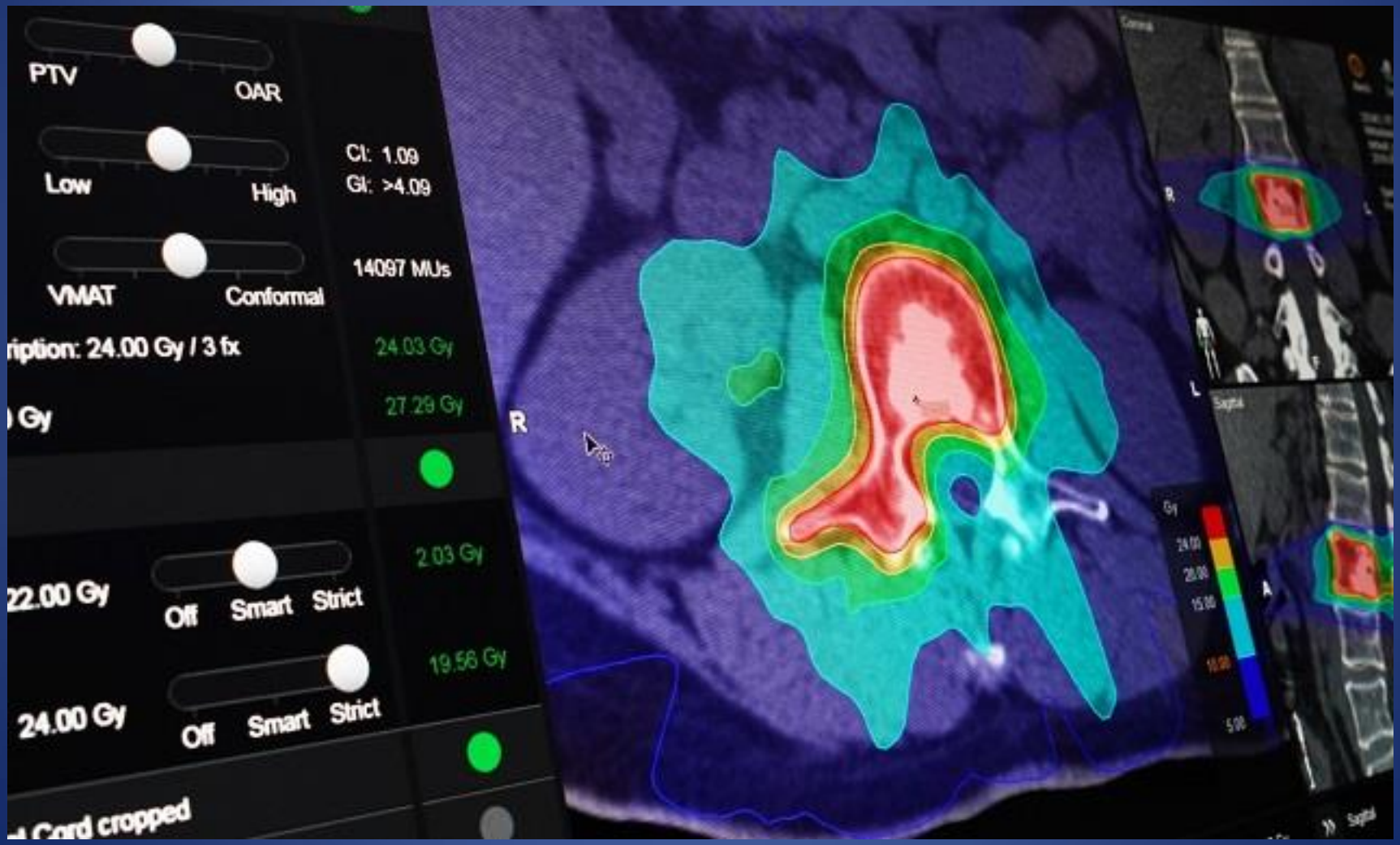
NCCN Guidelines

Regimen for Definitive Therapy	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
	Very-Low[1]	Low[1]	Favorable or good prognostic[2] intermediate	Unfavorable, or poor prognostic[2], intermediate	High and Very-High[3]	Node Positive
Beam Therapies						
72 Gy to 80 Gy at 2 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
75.6 Gy to 81.0 Gy at 1.8 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
70.2 Gy at 2.7 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
70 Gy at 2.5 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
60 Gy at 3 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
51.6 Gy at 4.3 Gy per fraction	✓	✓	✓			
37 Gy at 7.4 Gy per fraction	✓	✓	✓			
40 Gy at 8 Gy per fraction	✓	✓	✓			
36.25 Gy at 7.25 Gy per fraction	✓	✓	✓			

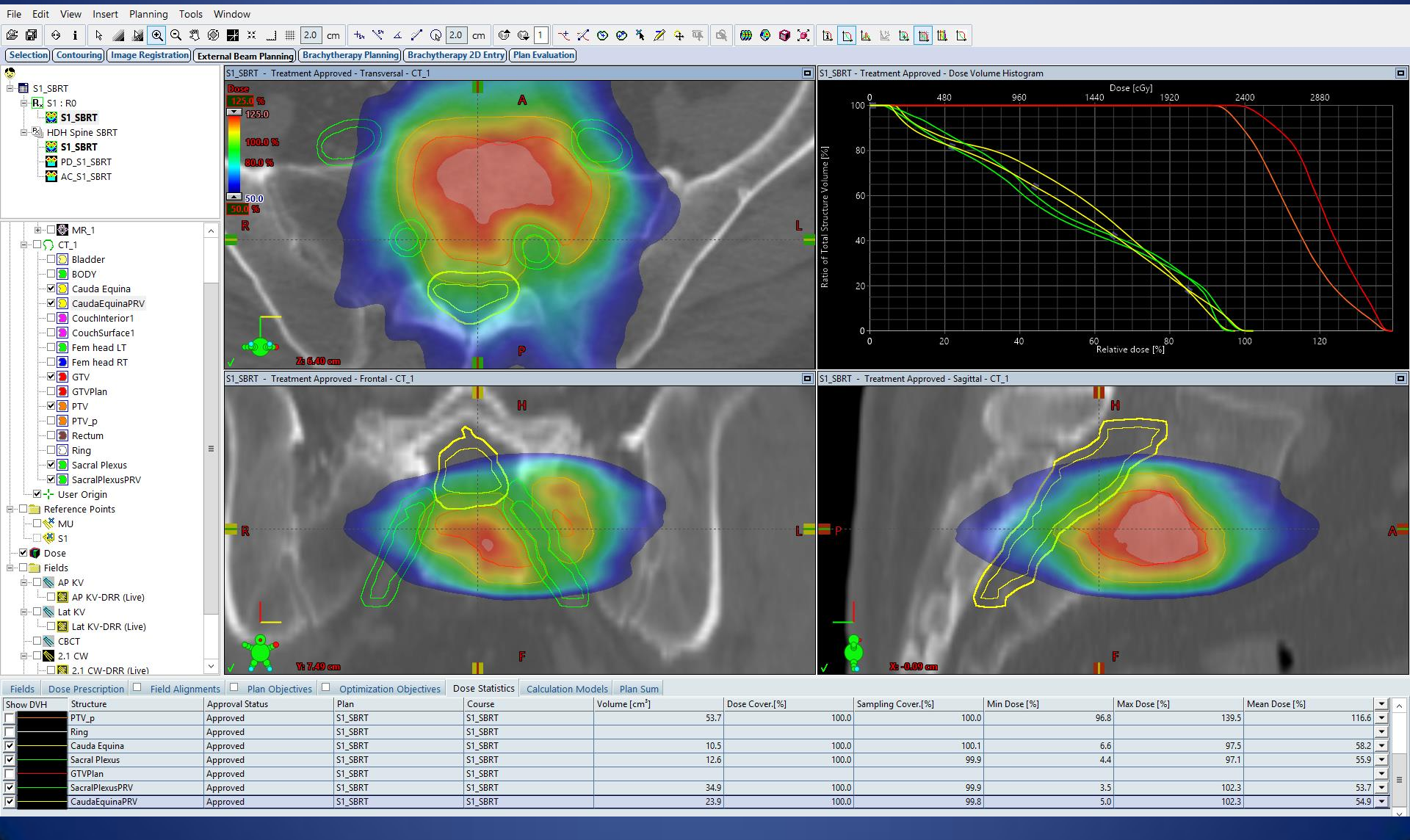
SABR for Metastatic Disease

- Traditional RT for metastases (bone, lymph nodes) is palliative (intended to relieve symptoms)
- SABR can be used for oligometastatic disease
- Oligometastatic disease refers to 4 or fewer small areas of involvement
- Goal of SABR ablative rather than merely palliative
- Typically 3 treatments

Spine Radiosurgery



Spine Radiosurgery



SABR Delays Progression

- Recent clinical trial randomized patients with oligometastatic disease to observation vs. metastasis directed treatment (surgery or SABR)
- MDT *nearly doubled* time to progression (defined as PSA rise requiring androgen deprivation therapy)

J Clin Oncol. 2018 Feb 10;36(5):446-453. doi: 10.1200/JCO.2017.75.4853. Epub 2017 Dec 14

Conclusions

- SABR/SBRT now part of NCCN guidelines for primary treatment of low-risk prostate cancer
- Although a “newer” technique, 5 year results appear comparable to longer treatment regimens
- Side effects usually mild
- SABR can significantly prolong time to progression in patients with limited metastatic disease

THANK YOU!