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Preface

We are proud to introduce the second edition of the *Radiation Oncology Self-Assessment Guide*, now titled *Radiation Oncology Board Review and Flashcard App*. The first edition, edited by John Suh, MD, and published in 2012, provided a comprehensive overview of the field of radiation oncology in an easy-to-digest flashcard format. Based on the feedback we received from many individuals who purchased the first edition, we have updated the print format and design and, in addition, Demos Medical Publishing and HLT have developed and included a flashcard app for quick mobile access and study on smartphones, tablets, and other devices.

In an era when the doubling time of medical knowledge is estimated to be 73 days, it has become increasingly difficult for even the most diligent resident or practicing physician to stay current. Since the publication of the last edition, we have seen hypofractionation become the standard of care for many patients with breast and prostate cancer, new data guiding the use of stereotactic radiosurgery and stereotactic body radiation therapy across multiple disease sites, an increase in the utilization of advanced treatment planning and delivery techniques, and the rise of immunotherapy, just to name a few. Organized by treatment site, detailed question sets have been thoroughly revised to provide up-to-date information on the natural history, epidemiology, diagnosis, staging, treatment options, and treatment-related side effects for each cancer type.

The format has been designed to efficiently test and reinforce knowledge of key concepts, critical studies, and major clinical guidelines, with the most important citations included. The new companion app allows the reader to easily access and navigate these study materials on the go. From trainees preparing for their board exams to practicing physicians looking for a review or preparing for the maintenance of certification exam, whether it be a few minutes between patients or a dedicated study session, we believe *Radiation Oncology Board Review and Flashcard App* Second Edition will continue to be an invaluable resource to the radiation oncology community.

Michael A. Weller, MD
Nikhil Joshi, MD
Anthony Mastroianni, MD, JD, MBA
Share
Radiation Oncology Question Review, Second Edition
1. What is the circulating half-life of PSA in a normal male?

PSA is generally accepted as having a half-life of 2 to 3 days.

2. What has been the effect of PSA screening upon the incidence and stage distribution of patients with prostate cancer?

The incidence of prostate cancer increased dramatically, more than doubling in the years after screening (from 100/100,000 people to over 240/100,000 people). The stage distribution has likewise changed, with a far greater percentage of patients presenting with early-stage disease and only 4% of patients presenting with metastatic disease.


3. Does PSA screening improve prostate cancer–specific mortality?

This is controversial. There have been three large randomized trials investigating PSA screening. Two European trials showed improvements in prostate cancer–specific mortality (though the number needed to screen to prevent one prostate cancer death is high), while the PLCO cancer screening trial showed no benefit. The results of the PLCO are criticized given the majority of men in the control (no PSA) arm actually underwent screening. No study has shown an overall survival benefit. Given the conflicting data and potential harms associated with overdiagnosis, there is some controversy over who should be screened. The latest recommendations from the USPSTF suggest individualized decision making for men between 55 and 69 years old, and against screening in men aged 70 and older.


4. Along with stage migration, have there been other changes in the way we assess important prognostic disease parameters (i.e., Gleason score) over time?

Yes, as part of the Connecticut Tumor Registry over 1,800 biopsy slides originally scored in 1990 to 1992 were rereviewed between 2002 and 2004 and the average Gleason score increased by almost a full point (from
5.95 to 6.8) for the same slides. Gleason score migration over time must be accounted for when comparing treatment results from different time frames across studies.


5. What did the PCPT assess?

The trial assessed the effectiveness of finasteride, a 5-alpha reductase inhibitor, in preventing prostate cancer compared to placebo in men greater than 55 years old with PSA ≤3 ng/mL, normal DRE, and AUA less than 20.


6. What were the results of the Prostate Cancer Prevention Trial?

The incidence of prostate cancer was lower in the finasteride arm (10.5% vs. 14.9%), but there was no difference in the incidence of high-grade (Gleason score 7 or higher) cancers, and no difference in 15-year survival between the two arms.

This is consistent with the results of the REDUCE trial, which randomized men to dutasteride versus placebo. Taken together, these trials suggest that 5-alpha reductase inhibitors may decrease the risk of developing low-grade prostate cancer, without impacting the incidence of high-grade cancer or mortality.


7. What is the AUA score, what is its range, and what does it measure?

AUA score to assess urinary function was developed for BPH. It was used to assess urinary function in prostate cancer. Scale is out of 35 with a lower score being less symptomatic.

8. What lymph node chains are included in nodal staging for prostate cancer (and covered during targeted pelvic nodal radiation)?

Internal iliac (hypogastric), external iliac (to junction of common iliac), obturator, and presacral (S1-S3).


9. In the AJCC 8th edition, if a biopsy confirms prostate cancer in a regional lymph node, what stage is the patient?

The patient would have N1 nodal staging, which makes them stage IVA. In the 8th edition, stage IV has been separated into IVA for patients with regional nodal metastases, and IVB for all other metastases.


10. What is the M-staging for adenocarcinoma of the prostate?

As defined by the AJCC 8th edition:

- M1a is involvement of non-regional lymph nodes.
- M1b is metastases to bone.
- M1c is metastases to other sites.


11. What are the Roach equations for risk of ECE, seminal vesicle, and pelvic lymph node involvement?

ECE: Risk (%) = \( \frac{3}{2} \times \text{PSA} + 10 \times (\text{Gleason-3}) \)

Seminal vesicle: Risk (%) = \( \text{PSA} + 10 \times (\text{Gleason-6}) \)

Lymph nodes: Risk (%) = \( \frac{2}{3} \times \text{PSA} + 10 \times (\text{Gleason-6}) \)


12. Given stage migration of prostate cancer over time and other variables, how reliable are the Roach formulas in modern patients?

There has been some suggestion in several reviews of modern surgical pathology that the rates of nodal positivity may be substantially lower than those predicted by the Roach formulas. This may influence treatment decision for today’s patients.


**PROSTATE CANCER—LOW RISK**

13. What is the evidence to support treatment of early-stage prostate cancer versus observation?

This is controversial. Swedish study SPCG-4 randomized 695 men with T1-2 (most were T2) prostate cancer with PSA less than 50 to radical prostatectomy versus watchful waiting. At 18 years, the RP arm had improved local control, distant metastases, prostate cancer-specific survival, and overall survival.

The PIVOT trial randomized 731 men with T1-2 prostate cancer with PSA less than 50 (most were T1, lower PSA values than SPCG-4) to radical prostatectomy versus observation. At 12.7 years median follow, the RP arm had fewer deaths due to prostate cancer (7.4% vs. 4%, *p* = .06), and lower all-cause mortality (61.3% vs. 66.8%, *p* = .06), but neither outcome reached statistical significance. On subgroup analysis, there was an improvement in all-cause mortality in men with intermediate-risk disease.


14. What is the evidence to support treatment of prostate cancer versus active surveillance?

The ProtecT trial randomized 1,643 men with localized prostate cancer to active surveillance, radical prostatectomy, or radiation therapy with ADT. Both intervention groups improved the rates of clinical progression and metastatic progression, but there were no differences
in prostate cancer specific or overall survival. Approximately 30 men needed to be treated to prevent one patient from developing metastatic disease.


15. **What are the outcomes with active surveillance?**

The Klotz study was a cohort of 933 men with low- and intermediate-risk prostate cancer (84% Gleason 3 + 3, 13% Gleason 3 + 4) who were followed under active surveillance. PSA was performed every 3 months for 2 years, and every 6 months thereafter. Repeated biopsy was performed with 12 months of diagnosis, and then every 3 to 4 years until age 80. Treatment was triggered by histologic upgrade on repeat biopsy, clinical progression on DRE, or PSA doubling time of less than 3 years. At a median follow up of 6.4 years, there were 15 deaths from prostate cancer (1.5%) and 13 additional patients developed metastatic disease (total of 2.8%). At 5, 10, and 15 years, 75.7%, 63.5%, and 55.0% of patients remained untreated on active surveillance.


16. **What are the Epstein criteria for prostate cancer and how are they used?**

- Cancer not felt on digital rectal examination (stage T1a-c)
- PSA density ≤0.1
- Gleason score is 6 or less with no Gleason pattern 4 or 5
- No more than two cores with cancer, or cancer involving no more than 50% of any core on a prostate biopsy

PSA density defined as total serum PSA divided by ellipsoid volume of prostate gland (length × width × height × 0.52). The Epstein criteria were developed to predict for “clinically insignificant prostate cancer on surgical pathology” (tumor <0.5 mL), however, they are informally used as conservative criteria for active surveillance at some centers. Older age (age >65 years) or medical comorbidities have also been added to the criteria.

17. In low-risk prostate cancer patients, what are the possible treatment recommendations?

Active surveillance in select patients (biannual PSA, annual DRE, with prostate biopsy every 1–4 years depending on institutional standard)
- Radical prostatectomy
- Prostate brachytherapy alone
- External beam radiation therapy alone

Prostate Cancer Version 2, 2018. NCCN Guidelines 2018

18. When evaluating a DVH and dosimetric plan, what normal tissue and target-dose constraints are considered acceptable?

- Cover PTV with at least 98% of the prescribed dose, coldest 0.03 mL to 95%
- Rectum—V70 less than 20% to 25%, V60 less than 50% (if covering nodes), V50 less than 50% (without nodes)
- Small bowel—maximum point dose of 52 Gy
- Bladder—V70 less than 25%, V55 less than 50%
- Femoral heads—V50 less than 5%
- Penile bulb—as low as possible, mean dose less than 52.5 Gy

http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0815

19. Is there evidence to support radiation dose escalation in prostate cancer?

At least five randomized trials have been performed using a variety of techniques. They have consistently demonstrated improved biochemical control, worse toxicity, and no difference in survival.


20. Which groups benefited from dose-escalated radiation in the Pollock dose-escalation phase III trial?

Predominantly patients with PSA greater than 10, though in update bRFS was improved in patients with low-risk disease as well.

<table>
<thead>
<tr>
<th></th>
<th>Overall and 5-y FFF/8-y FFF</th>
<th>PSA &gt;10 and 5-y FFF/8-y FFF</th>
<th>PSA ≤10 and 5-y FFF/8-y FFF</th>
<th>Low-Risk and 8-y FFF</th>
<th>5-y OS/6-y OS</th>
<th>Gr 3 Rectal Toxicity (at 6 y)</th>
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<tbody>
<tr>
<td>70 Gy</td>
<td>69%/50%</td>
<td>48%/28%</td>
<td>~80%/60%</td>
<td>63%</td>
<td>~90%/83%</td>
<td>17%</td>
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<tr>
<td>78 Gy</td>
<td>79%/73%</td>
<td>75%/72%</td>
<td>~80%/74%</td>
<td>88%</td>
<td>90%/90%</td>
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<td>.011/.001</td>
<td>NS</td>
<td>.042</td>
<td>NS</td>
<td>.006</td>
</tr>
</tbody>
</table>


21. Was rectal toxicity increased by high-dose radiation in the Pollock dose-escalation phase III trial?

Yes, grade 3 and higher rectal toxicity was increased in the high-dose group, though this was found to have a significant correlation with rectal dosimetry in particular:

- When rectal V70 ≤25%, there was a 16% grade 2 or higher toxicity.
- When rectal V70 was greater than 25%, there was a 46% incidence of grade 2 or higher toxicity.


22. **On subset analysis of patients in the Pollack dose-escalation phase III trial, was any correlation found between biochemical control and rectal distension at the time of simulation (perhaps as a surrogate for potential interfraction motion)?**

Yes, patients with rectal distension at the time of simulation were found to have an increase in local failure. The larger the cross-sectional area of the rectum at planning, the greater the likelihood for failure. In addition, patients with a distended rectum at planning also had lower toxicity, further suggesting that rectal distension was not maintained during treatment, which resulted in the treatment being targeted too anteriorly. Of note no IGRT was used in this study. This may explain the local failure rate as changes in rectal distension may have caused geographical misses.


23. **Does the use of IGRT potentially address the concern of increased biochemical failure in patients with distended rectum at the time of simulation?**

Yes, a review of patients treated with BAT ultrasound-guided IGRT at the Cleveland Clinic found no influence of rectal volume on outcome for patients of all risk groups.


24. **How was the radiation delivered in the Zietman PROG 95-09 phase III study on dose escalation for prostate cancer?**

Patients received a high- or low-dose proton boost, followed by 3D conformal radiation on the PROG 95-09 trial.

A boost was first delivered via proton beam to 19.8 GyE or 28.8 GyE (applied proton beam dose was corrected to photon equivalent using a RBE of 1.1). CTV was prostate +5 mm margin with PTV an additional 7 to 10 mm. All patients then received conformal EBRT to 50.4 Gy with CTV prostate +SVs.

25. What were the results and conclusion of the Zietman PROG 95-09 phase III study?

The study demonstrated a biochemical advantage to high-dose radiation for patients with clinically localized prostate cancer. Five-year FFF for low-risk prostate cancer patients (PSA ≤10, <T2a, GS <6) was 60.1% and 80.5% in the 70.2 GyE and 79.2 GyE arms, respectively. There were also 5-year LC and overall 5-year FFF for all patients included. This was the first randomized trial to demonstrate an advantage to dose-escalation in the low-risk group on subset analysis (though it was not specifically powered for this).

<table>
<thead>
<tr>
<th></th>
<th>Overall 5-y FFF</th>
<th>5-y LC</th>
<th>5-y FFF Low Risk: PSA ≤10, &lt;T2a, GS &lt;6</th>
<th>5-y OS</th>
<th>Acute/Late Gr 2 GI toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.2 GyE</td>
<td>61.4%</td>
<td>47.6%</td>
<td>60.1%</td>
<td>97%</td>
<td>8%</td>
</tr>
<tr>
<td>79.2 GyE</td>
<td>80.4%</td>
<td>67.2%</td>
<td>80.5%</td>
<td>96%</td>
<td>41%</td>
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<td>&lt;.001</td>
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<td></td>
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<td>.005</td>
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</table>


26. Is there a benefit to using IMRT over a conventional four-field box or 3D conformal radiation?

While there has not been evidence for a difference in disease control, toxicity appears to be reduced by the use of IMRT. In an MSKCC study, there was a reduction in the rate of grade 2 or higher GI toxicity comparing IMRT with conventional techniques despite the use of greater radiation dose in the IMRT group—13% versus 5%, respectively. Analysis of the high-dose arm of RTOG 0126 (a phase III trial comparing high-dose to standard-dose radiation, allowing for either 3D-CRT or IMRT) also seems to suggest lower GI toxicity with the use of IMRT (though tighter margins were used for the IMRT patients).


27. What are the results of RTOG 0126?

RTOG 0126 randomized 1,532 men with low- and intermediate-risk prostate cancer to 70.2 Gy versus 79.2 Gy (using 3D conformal RT or IMRT). With a median follow-up of 8.4 years, there was no difference in overall survival between arms (primary endpoint). Dose escalation did improve biochemical control, and decreased 8-year cumulative rates of distant metastases (4% vs. 6%, \( p = .05 \)). Dose escalation was associated with higher grade 2 or greater late GI toxicity (21% vs. 15%) and late GU toxicity (12% vs. 7%).


28. Is there evidence to support use of moderate hypofractionation for prostate cancer?

Multiple randomized trials have been published that suggest no difference in oncologic outcomes and similar toxicity profiles with moderate hypofractionation, particularly for low- and intermediate-risk prostate cancer. Potential regimens include 70 Gy delivered over 28 fractions (2.5 Gy/fx) from RTOG 0415, and 60 Gy in 20 fractions (3 Gy/fx) from the CHHiP and PROFIT trials.


29. What are the results of RTOG 0415, a study investigating moderate hypofractionation for low-risk prostate cancer?

RTOG 0514 randomized 1,115 men with low-risk prostate cancer to in 41 fractions (1.8 Gy/fx) versus 70 Gy in 28 fractions (2.5 Gy/fx). At a median follow-up of 5.8 years, there was no difference in the primary endpoint of disease-free survival (86.3% vs. 85.3%). There was also no difference in biochemical relapse or overall survival. Clinical reported
late grade 2 GI and GU toxicity were slightly higher with hypofractionation, but there was no difference in patient-reported outcomes for bowel, urinary or sexual function between arms.


### 30. What are the results of the CHHiP trial, a noninferiority study investigating moderate hypofractionation for prostate cancer?

CHHiP was a noninferiority study with three arms: 74 Gy in 27 fractions (2 Gy/fx), 60 Gy in 20 fractions (3 Gy/fx), and 57 Gy in 19 fractions (3 Gy/fx). 3,216 men were randomized. At 5.2 years median follow-up, the 60 Gy arm was found to be noninferior to standard fractionation, with failure-free rates of 90.6% and 88.3%, respectively. The 57 Gy arm did not meet criteria for noninferiority. Both physician and patient reported late GI, GU, and sexual side-effect profiles were similar across treatment arms.


### 31. What are the results of the PROFIT trial, a noninferiority study investigating moderate hypofractionation for prostate cancer?

CHHiP was a randomized noninferiority study of 1,206 patients. Men with intermediate-risk prostate cancer were randomized to standard fractionation of 78 Gy in 39 fractions versus 60 Gy in 20 fractions. At a median follow-up of 6 years, the 60 Gy arm had similar biochemical-clinical failure (85% in both arms), meeting the noninferiority threshold. There was no difference in overall survival, and both physician and patient reported late GI and GU toxicities were similar across treatment arms.

32. What are important dose constraints for prostate brachytherapy?

**Preplan:** For I-125, generally accepted dosimetric parameters to the preimplant plan planning target volume include the following:

- D90 110% to 120% of prescription
  - V100 greater than 99%
- V150 less than 60%
  - V200 less than 20%
- Urethra less than 150% of prescription

For Pd-103

- D90 110% to 120% of prescription
  - V100 greater than 99%
- V150 less than 70%
  - V200 less than 30% to 40%
- Urethra less than 150% of prescription

**Postplan:**

- D90 greater than 130 to 140 Gy for I-125
- D90 greater than 110 to 120 Gy for Pd-103
- V100 greater than 75%
- 1 mL Rectum less than 100% of prescription dose

In a 2002 publication, Stock reported that D90 less than 140 Gy associated with decreased biochemical control. D90 greater than 180 Gy associated with increased long-term urinary symptoms.


33. What is the half-life of I-125 and Pd-103?

I-125—60 days  
Pd-103—17 days  


34. Is there a difference in outcome between I-125 and Pd-103 for LDR prostate brachytherapy?

No, based on a randomized trial of I-125 versus Pd-103 implant. This trial enrolled 126 patients. Patients treated with palladium did have a higher intensity of acute side effects with subsequent faster resolution, likely due to a higher dose rate, but there was no evidence for a difference in outcome.


35. In what setting is prostate brachytherapy appropriate as monotherapy?

Per NCCN, brachytherapy alone is appropriate for low-risk and “good” intermediate-risk prostate cancer. There is considerable controversy over its use in “poor” intermediate-risk and high-risk disease. Of note, RTOG 0232 was a randomized study comparing brachytherapy alone versus brachytherapy + supplemental EBRT for intermediate-risk prostate cancer, and its initial report in abstract form, demonstrated no advantage to the addition of EBRT, with increased late toxicity.

Prestidge, RTOG 0232. Abstract 7 presented as ASTRO 2016.

36. In what setting is prostate brachytherapy appropriate with EBRT?

Prostate brachytherapy boost can be considered in patients with “poor” intermediate-risk and high-risk disease per NCCN guidelines. The ASCENDE RT trial showed improved biochemical control, higher GU
toxicity, and no difference in survival with the addition of brachytherapy boost to RT + ADT in men with intermediate- and high-risk (69%) disease.


Prostate Cancer Version 2.2018. NCCN Guidelines 2018

37. What are American Brachytherapy Society guideline exclusion criteria for brachytherapy?

Absolute contraindications include patients unable to tolerate general or spinal anesthesia, life expectancy of less than 10 years, and presence of metastases.

Relative contraindications to brachytherapy per ABS guidelines include high IPSS score for irritative/obstructive symptoms, prostate greater than 60 mL, large or poorly healed TURP defect, inflammatory bowel disease, prior pelvic radiation, and median lobe hypertrophy, although institutional phase II data from select centers demonstrate acceptable outcomes for patients beyond size criteria, select patients s/p TURP, and patients with moderate median lobe hypertrophy.


38. After prostate implant, does any PSA rise represent recurrent tumor?

It is important to look at the pattern of PSA rise after a nadir. If the rise is within 3 years, it may represent a PSA bounce. It could also represent residual untreated prostate cells if the rise is very slow or even residual/recurrent prostate cancer. Most rises within 3 years are due to PSA bounce and resolve spontaneously, while rises beyond 3 years typically portend recurrent/metastatic disease.

39. How does brachytherapy monotherapy compare to prostatectomy and external beam radiation for disease-specific outcomes in low- and intermediate-risk prostate cancer?

There are no randomized data of sufficient volume comparing brachytherapy monotherapy to EBRT or prostatectomy. Several retrospective series suggest similar outcomes for biochemical and cancer-free survival in low- and intermediate-risk patients with the use of these modalities. An attempt by the Prostate Cancer Results Study Group to synthesize the literature suggested that for low-risk patients brachytherapy provides superior biochemical progression-free survival, and for intermediate-risk patients RT + brachytherapy appears similar to brachytherapy alone.


PROSTATE CANCER—HIGH RISK

40. What are the classes of androgen deprivation used for prostate cancer?

LHRH agonists, antiandrogens (nonsteroidal, steroidal), and 5-alpha reductase inhibitors.


41. What are the major short-term and long-term side effects of androgen deprivation with an LHRH agonist?

Short term: fatigue, hot flashes, insomnia, decreased libido, and irritability.
Long term: metabolic side effects (dyslipidemia, coronary artery disease, diabetes, insulin resistance, obesity), decreased bone density, decreased muscle mass, gynecomastia, anemia, mood changes, insomnia, and fatigue.

42. What organ(s) are responsible for testosterone production, and approximately what percentage of circulating testosterone do they produce in a normal male?

Testicles (90%), adrenals (10%).


43. Is there an advantage to radiation in addition to lifelong hormones for patients with high-risk prostate cancer?

Yes, there is an overall survival advantage demonstrated in two prospective randomized trials.

A randomized Swedish study (Widmark) of lifelong androgen deprivation therapy with or without radiation therapy in patients with palpable disease (78% T3) demonstrated improved 10-year cancer-specific (88.1% vs. 76.1%) and overall (70.4% vs. 60.6%) survival for the addition of radiotherapy. There were slightly more urinary symptoms and erectile dysfunction, but overall quality of life was similar between the two based on patient questionnaires. This has been corroborated in similar smaller series.


44. Is there a benefit to the addition of androgen deprivation to EBRT for locally advanced prostate cancer (and if so, what is the level of benefit)?

Randomized trials including mostly patients with T3 disease (plus other subsets of palpable, locally advanced, and node-positive patients) have demonstrated improvements in overall survival (10%–20%) for some trials (i.e., EORTC 22863 and RTOG 85-31), or at least disease-specific survival and distant metastasis in others (RTOG 86-10).

| EORTC 22863: 70 Gy EBRT +/- 3 Years Goserelin and 1-Month Cyproterone Acetate |
|---|---|---|---|
| 10-y Data | Overall Survival | Clinical Progression-Free Survival | Biochemical Progression-Free Survival |
| EBRT + AD | 58.1% | 47.7% | 37.9% |
| EBRT alone | 39.8% | 22.7% | 17.6% |
| p-value | .0004 | <.0001 | <.0001 |
RTOG 85-31: 64–70 Gy EBRT +/− 2 Years to Lifetime Goserelin (Included 15% Node + Patients and Some Postop as Well)

<table>
<thead>
<tr>
<th></th>
<th>Metastasis</th>
<th>PSA &lt;1.5</th>
<th>Disease-Specific Survival</th>
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<tr>
<td>EBRT + AD</td>
<td>24%</td>
<td>31%</td>
<td>84%</td>
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</table>

RTOG 86-10: 64–70 Gy EBRT ± 4 Months Goserelin and Flutamide

<table>
<thead>
<tr>
<th></th>
<th>Local Failure</th>
<th>Biochemical Failure</th>
<th>Distant Metastasis</th>
<th>Disease-Specific Survival</th>
<th>Overall Survival</th>
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<tr>
<td>EBRT + AD</td>
<td>30%</td>
<td>65%</td>
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<td>76%</td>
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**45. Is there evidence for a benefit to the addition of androgen deprivation to EBRT for patients who are at high risk by modern disease parameters (i.e., PSA and Gleason score)?**

Yes, D’Amico randomized patients with prostate cancer (cT1b-T2b and either PSA 10–40 ng/mL or Gleason 7–10 or ECE/SV invasion by MRI) to EBRT (70 Gy) +/− 6 months of androgen suppression (goserelin or leuprolide + flutamide) beginning 2 months prior to EBRT.

The addition of androgen suppression improved 8-year overall survival from 61% to 74%, and also improved biochemical control, freedom from salvage hormones, and cancer-specific survival. In the most recent update at 16.6 years of follow-up, the survival benefit persisted in men with no or minimal comorbidity, but in men with moderate to high comorbidity, the addition of ADT resulted in worse overall mortality.

46. Is there evidence for a benefit to the addition of androgen deprivation to EBRT for patients who received dose-escalated radiation therapy?

Yes. EORTC 22991 was a prospective randomized trial of 819 men with intermediate- or high-risk prostate cancer who were randomized to RT +/- 6 months of ADT. RT doses of 70 to 78 Gy were allowed. The addition of ADT improved biochemical and clinical progression-free survival (overall survival data not yet mature), and an exploratory analysis suggested the effect was similar across radiation dose groups. Additionally, the DART trial showed improved outcomes with 28 months of ADT versus 4 months, both with dose-escalated RT of at least 76 Gy.


47. Is there any randomized evidence to support long-term (vs. short-term) androgen deprivation in locally advanced prostate cancer?

Yes, though the optimal duration of ADT is not clear. Two randomized trials of short- (4–6 months) versus long-term (28–36 months) androgen deprivation have demonstrated improved outcomes for locally advanced prostate cancer patients receiving long-term androgen deprivation therapy. RTOG 92-02 demonstrated improvements in biochemical failure, distant metastasis, and disease-specific survival, however, no significant benefit to overall survival. EORTC 22961 demonstrated improvement in all endpoints for long-term androgen deprivation.

<table>
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<th>RTOG 92-02</th>
<th>Disease-Free Survival</th>
<th>Biochemical Failure</th>
<th>Local Failure</th>
<th>Distant Metastasis</th>
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<td>.0002</td>
<td>.0001 (Gleason 2-7 p = NS)</td>
<td>.25 (GS 8+, p = .044)</td>
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### EORTC 22961

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<th>5-y Data</th>
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### 48. Is there any randomized evidence to support long-term (vs. short-term) androgen deprivation in patients treated with dose-escalated RT?

Yes. The DART trial randomized 178 men with intermediate and high-risk prostate cancer to RT with short-term ADT (4 months) versus RT with long-term ADT (28 months). RT dose was 76 to 82 Gy. At 5 years, long-term ADT improved biochemical disease-free survival (89% vs. 81%), distant metastases-free survival (94% vs. 83%), and overall survival (95% vs. 86%).


### 49. What are the results of the ASCENDE-RT trial investigating a brachytherapy boost?

ASCENDE-RT was a phase III trial of 398 men with intermediate- and high-risk prostate cancer randomized to RT and ADT +/- brachytherapy boost. About 70% of men had high-risk disease. ADT was given for 12 months, and the RT dose was 46 Gy to the pelvis followed by an RT boost to 78 Gy or a brachy boost. At a median follow up of 6.5 years, the addition of brachytherapy improved biochemical control (86% vs. 75% at 7 years, 83% vs. 62% at with no change in overall survival. Brachytherapy
boost resulted in higher grade 3+ GU toxicity (18.4% vs. 5.2%) and a statistically significant decline in physical function and urinary function scales in patient reported quality of life.


50. What is the recommended PSA follow-up for patients after completion of radiation treatment?

PSA blood work every 6 months to optimize sensitivity and specificity of possible biochemical failure. This should take place with follow-up H&P.


51. For patients that have biochemical failure after definitive treatment for their prostate cancer, what is the median time to development of a bony metastasis and subsequently death from prostate cancer?

This is highly variable based on patients, era of treatment (available agents for treatment), and Gleason score + PSA kinetics. A review by Freedland suggested a very wide range of 4 to - 15+ years for survival following biochemical failure. Pound suggest a median of 8 years to development of bony metastases and 5 additional years to death from prostate cancer (though again with a large degree of variability).


PROSTATE CANCER—ADJUVANT AND SALVAGE RADIATION

52. Where are the most common sites of local recurrence s/p prostatectomy?

Perianastoamotic (63%), bladder neck (10%), retrovesical (17%), and other (10%).


53. What are the four most favorable factors from the Stephenson nomogram to predict biochemical outcome of salvage radiation?

Pre-RT PSA less than 2 ng/mL (the lower the better), surgical margins positive, Gleason score ≤7, and PSA doubling time greater than 10 months. An updated nomogram from Tendulkar demonstrated improved biochemical control and decreased distant metastases when patients were treated at even lower levels (below 0.2 ng/mL), reflective of the modern treatment era.


54. Which patients appear to derive the greatest benefit in cancer-specific survival from salvage radiation?

Patients who appear to derive the greatest benefit are those with rapidly progressive disease, though still close to time of initial biochemical failure (i.e., perhaps those with high-risk disease caught before metastasis). Benefit to salvage radiation was greatest in men with PSA doubling time ≤6 months, and no benefit was seen in those who received salvage RT ≥2 years after initial biochemical failure.

55. **What is the benefit of adjuvant radiation for prostate cancer s/p prostatectomy with pathological findings of extracapsular extension, positive margins, or involved seminal vesicles?**

Improvement in local and biochemical control (from approximately 50% to 75%) was seen consistently in three randomized trials (EORTC 22911, SWOG 8794, and ARO 96-02).

Distant metastasis and overall survival were improved in the 10-year update of the SWOG trial, however, no statistically significant difference was seen in the 10-year update of the EORTC trial or ARO trials.


56. **What is the magnitude of the survival benefit for adjuvant radiation in the SWOG study after radical prostatectomy?**

10-year overall survival 66% (salvage) versus 75% (adjuvant RT).

Median 13.3 years (salvage) versus 15.2 years (adjuvant).


57. **What was the median PSA at the time of salvage radiation in the SWOG trials?**

1.0 (in the 80% of patients with PSA available within 6 months of starting radiation therapy).

58. Is there a difference between adjuvant radiation versus early salvage radiation after prostatectomy?

There is some controversy about the interpretation of the adjuvant RT trials in the ultrasensitive PSA era, and randomized comparisons with early salvage RT are underway. In the meantime, a large propensity matched cohort with over 1,500 patients demonstrated improved outcomes with adjuvant RT, including overall survival.


59. What evidence exists for hormone treatments in the salvage radiation setting?

Two randomized trials have demonstrated a benefit to the addition of ADT:

RTOG 9601 evaluated post-RP patients with pT3N0 or with pT2N0 and positive margins with elevated PSA. Patients were randomized to RT alone (64.8 Gy in 1.8 Gy fractions) versus RT + 24 months of bicalutamide, 150 mg daily during and after RT. At the 12-year follow-up, the addition of bicalutamide significantly improved biochemical control, reduced distant metastases (14% vs. 23%), decreased prostate cancer-specific mortality (6% vs. 13%), and improved overall survival (76% vs. 71%).

GETUG AFU 16 randomized with initially undetectable PSA after prostatectomy and a subsequent rise to between 0.2 and 2.0 ng/mL to RT (66 Gy in 2 Gy fractions) +/- ADT with 6 months of goserelin. At 5 years, the additional of ADT improved biochemical control, and other endpoints continue to mature.


60. What dose should be used for adjuvant and salvage radiation?

The radiation doses on the three randomized adjuvant trials were 60 to 66 Gy and in the salvage setting, a dose of 70 Gy is typically used (and recommended, but not standardized in the adjuvant trials).


**NODE-POSITIVE PROSTATE CANCER**

61. **For surgically resected patients found to be lymph node positive, is there evidence for initiation of immediate androgen deprivation?**

Yes, the Messing randomized trial demonstrated a survival advantage to immediate versus delayed lifelong androgen deprivation for histologically proven node-positive patients status postprostatectomy (though it is sometimes criticized for extremely late use of hormonal therapy in the observation group).


62. **For histologically proven node-positive patients treated with radiation is there evidence to support the upfront addition of androgen deprivation therapy?**

Yes, a subset analysis of RTOG 85-31 included 173 histologically node-positive patients treated with EBRT, with or without hormonal therapy. The 5-year progression-free survival was significantly increased (54% vs. 33%) by androgen deprivation compared to patients randomized to receive hormonal therapy at the time of relapse.


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63. Is there evidence to support the addition of radiation following discovery of positive lymph nodes at time of radical prostatectomy?

Several phase II studies of adjuvant prostate bed and pelvic radiation with concurrent androgen deprivation suggest outcomes which appear better than observation or lifelong androgen deprivation, and a European matched-pair analysis suggests a potential survival benefit.


URETHRAL CANCER

64. What is the most common histology for cancer of the urethra?

This varies by anatomic site. Transitional cell carcinoma and adenocarcinoma typically arise in the proximal urethra. Although squamous cell carcinoma predominates in the distal (penile) urethra, it can arise in any segment, particularly in patients with a history of chronic inflammation. Squamous cell carcinoma is thought to be most prevalent (75% of urethral cancer), though some series describe a high percentage of TCC as well. Histology may be related to the underlying risk factors of the population (i.e., chronic inflammation vs. HPV).


65. Invasion of which structures would stage a urethral cancer as T3?

Corpus cavernosum, periprostatic fat, or anterior vagina.


66. What is the N staging for urethral cancer?

- N0—no nodal metastasis
- N1—metastases to single LN
- N2—multiple positive LNs

67. Which lymph node groups do urethral cancers typically drain to?

Lymphatics from the proximal segment drain into the external and internal iliac, obturator, and presacral chains. Distal lesions drain to the superficial and deep inguinal lymph nodes.


68. What is the basic management plan for early versus locally advanced urethral cancer?

Early distal lesions are typically treated with surgery, local excision with goal of 2-cm margin.

Early proximal lesions (relatively rare as these are typically locally advanced) require more significant surgical management or definitive radiation.

Locally advanced tumors typically treated with combined modality therapy. One retrospective review found that neoadjuvant chemotherapy or chemoradiation improved outcomes compared to upfront surgery followed by chemotherapy in men with T3 or lymph node–positive disease.


69. How could one deliver definitive radiation for a bulbo-membranous urethral lesion?

Options include external beam radiation to the pelvis, tumor, and inguinal areas to 45 Gy followed by either a brachytherapy or external beam boost to gross disease (final target dose of 60–75 Gy). Alternatively, for a localized disease brachytherapy alone (likely using an interstitial implant/Syed template to a total dose of 60–65 Gy) could be considered.


70. How would one deliver radiation for a prostatic urethral cancer?

Very similar to treatment of prostate cancer, with pelvic nodal coverage to 45 Gy and cone down to tumor to high dose (can safely treat to 70–74 Gy given experience with prostate cancer).


PENILE CANCER

71. What changes were made in penile cancer staging in the AJCC 8th edition?

T1 tumors were subdivided based on anatomic site. T2 is now classified as invasion of the corpus spongiosum, with invasion of the corpus cavernosum upstaged to T3.


72. What is the risk of nodal disease for T1 and T2 penile cancer?

11% for T1, 63% for T2.


73. What are the risk factors for the development of penile cancer?

HPV infection (16 and 18), lack of childhood circumcision, penile lichen sclerosis, age, smoking, phimosis, and poor penile hygiene.


74. What is the most important prognostic factor for patients diagnosed with penile cancer?

LN status is the single most important prognostic factor. Five-year OS for LN− is 65%, whereas LN+ is 30%. High-grade, sarcomatoid, and basa-

loid subtypes have higher risk of nodal metastasis and poorer survival. Verrucous subtype has an excellent prognosis, though may be minimally responsive to radiation (primary management is surgical). Evidence for improved outcomes with HPV positivity is mixed.

75. What is the median survival with localized, regional, and metastatic penile cancer?

- Localized—4 years
- Regional—2.5 years
- Metastatic—7 months


76. If considering radiation, what is a potential critical preradiation anatomic factor to consider due to treatment-related edema/erythema?

Circumcision is typically recommended prior to treatment (without circumcision, skin reaction and lymphedema can be extreme during treatment).


77. What is the expected penile preservation rate for a T1–T3 penile cancer treated with brachytherapy to 60 Gy?

88% at 5 years, 67% at 10 years.


RENAL CELL CARCINOMA

78. What are the subtypes of renal cell carcinoma?

Clear cell, chromophilic, chromophobic, and collecting duct. Clear cell is associated with necrosis and is predictive of poorer prognosis. The Fuhrman nuclear grading system is also predictive of outcome.


79. Is there any role for definitive radiation for renal cell carcinoma?

In general no, particularly given the excellent tolerability of laparoscopic nephrectomy/partial nephrectomy. However, there have been multiple phase I and II studies investigating the use of SBRT, particularly in the...
medically inoperable population with favorable results. For example, a review of 10 studies treating 126 patients with 1-6 fraction SBRT found a local control of ~94% and the risk of grade 3 or higher toxicity less than 4%.


80. Is there an indication for adjuvant radiation for resected T3 or T4 renal cell carcinoma?

Typically no. Four randomized trials of neoadjuvant or adjuvant radiation have not revealed a benefit to radiation in combination with surgical resection (in fact, some demonstrate a detriment), though these trials used older radiation treatment techniques and targeting.


BLADDER CANCER

81. What changes to bladder cancer staging were made in the AJCC 8th edition?

M staging was subdivided into lymph node only metastases beyond the common iliac (M1a) and other distant metastases (M1b). Additionally, stage groups III and IV were subdivided: Group IIIA included T3a-T4a, N0, T1-T4a, and N1; Group IIIB included T1-T4a and N2-3; Group IVA included T4B, N0, M0, or any M1a; and Group IVB included any M1b.


82. What is the most common site for transitional cell carcinoma of the bladder (the most common histology)?

Trigone, followed by bladder neck.


83. What is the most common site for adenocarcinoma of the bladder?

Urachus (located at the remnant of the umbilical cord).

84. What is the general paradigm for treatment planning with radiation to the bladder?

Radiation is targeted to the entire bladder plus pelvic lymph nodes (40–46 Gy), followed by a cone down to the whole bladder (50–54 Gy), and a boost to the tumor + 2 cm (as defined by all available imaging + cystoscopy) to around 64 Gy.


85. What is the 5-year OS for patients treated with chemo radiation for bladder cancer?

A pooled analysis of prospective RTOG trials found 5-year OS to be 57%. OS varied by T stage (62% for T2, 49% for T3–4). This compares favorably with surgical series.


86. What is the CR rate after induction with cisplatinum-based chemoradiation?

Approximately 70% to 80% (patients with less than a complete response after induction chemoradiation should go on to salvage cystectomy).


87. In patients with a complete response to induction chemoradiation, what percentage will remain free of local recurrence and avoid cystectomy long term?

Approximately 85%.


88. What are the contraindications (relative or absolute) to bladder conservation treatment with chemoradiation?

- Multifocal tumor/CIS
- Tumor size greater than 5 cm
- T4
- Ureteral involvement
- Hydronephrosis
- Chronic cystitis
- Poor bladder function
- Node positive
- Metastatic disease


89. In patients treated with bladder preservation, what is the rate of grade 3 GI and grade 3 GU toxicity?

In a combined analysis of 4 RTOG trials, there is a 6% late grade 3 GU toxicity and 2% late grade 3 GI toxicity. No reported grade 4 or 5 toxicity.

90. Is there an advantage to neoadjuvant chemotherapy prior to chemoradiation for locally advanced bladder cancer?

No, per RTOG 8903. Patients were randomized to +/- neoadjuvant chemotherapy with methotrexate, cisplatin, and vinblastine, followed by chemoradiation to 64.8 Gy total.


91. Does adding chemotherapy to definitive RT improve outcomes in patients with bladder cancer?

Yes. The BC2001 study randomized 360 patients with T2–T4a bladder cancer to definitive RT +/- concurrent chemotherapy with 5-FU and mitomycin C. The addition of chemotherapy improved locoregional disease-free survival (67% vs. 54%) at 2 years. Overall survival at 5 years was improved from 35% to 48%, however, the study was not powered for this endpoint and this did not reach statistical significance.


92. How was the radiation delivered on the BC2001 study examining the addition of chemotherapy to definitive radiation in bladder cancer?

On BC2001, two fractionations were permitted. Physicians could elect to treat to 64 Gy in 32 fractions (2 Gy/fx) or 55 Gy in 20 fractions (2.75 Gy/fx). The target volume included the whole bladder + 1.5 cm margin, and any extravesical extent of tumor + 2 cm margin. The trial included a second randomization of reduced high-dose volume RT, where patients could be randomized to receive standard whole bladder RT versus a reduced high-dose volume technique. On the reduced high-dose arm, the whole bladder PTV received 80% of the prescribed dose, and the full dose was delivered to GTV + 1.5 cm margin. Though it did not meet the noninferiority margin, there appeared to be no differences in locoregional control or toxicity between the groups.


TESTICULAR CANCER

93. What are common risk factors for testicular cancer?

- CIS (50%), cryptorchidism (35 × baseline), undescended testis, previous testicular cancer within 5 years (2%-5%), infertility, and family history (father, 4 × baseline; brother, 8–10 × baseline).
- Klinefelter’s is associated with risk of mediastinal germ cell tumors.


94. What are the subtypes of germ cell tumors, and what are the associated tumor markers?

- Seminoma—may express β-HCG modestly (<100 ng/mL) in 15% of pure seminomas (due to syncytiotrophoblastic cells, no difference in treatment or prognosis from non-β-HCG expressing seminoma), if other markers expressed, pure seminoma is ruled out (though AFP can occasionally be from a liver source)
  - Classic Seminoma—most common
  - Anaplastic—more mitosis per high-power field than classic, in older series suggestion of worse prognosis, modern series suggest similar outcomes and treatment is the same as Classic Seminoma
  - Spermatocytic—rare subtype, seen predominately in men over 45 years old, not associated with CIS, almost never spreads to nodes therefore typically adjuvant treatment is not indicated
- Nonseminoma
  - Yolk sack tumor +AFP, −β-HCG
  - Choriocarcinoma −AFP, +β-HCG (typically extremely high)
  - Embryonal +AFP, +β-HCG
  - Teratoma variable, typically marker negative


95. What is the half-life of β-HCG and AFP?

- βHCG—1.5 to 2 days
- AFP—5 to 7 days

96. What is the risk of recurrence after orchiectomy for a stage I seminoma patient choosing to undergo observation tumors less than 3 cm? Greater than 3 cm?

Risk is ~12% for tumors less than 3 cm and 20% for tumors greater than 3 cm


97. For a patient with stage I seminoma undergoing adjuvant radiation, what is the 5-year relapse free and OS, and for those patients who do suffer relapse, where does relapse typically occur?

5-year OS 99%, 5-year RFS 97%.

Patterns of failure: 1% in pelvis, 1% in mediastinum/SCV, 1% distant (typically pulmonary).


98. What are the relative advantages of treating 20 Gy versus 30 Gy for adjuvant radiation for stage I seminoma with respect to tumor control and toxicity (based on the best available randomized evidence)?

On the MRC TE18/EORTC 30942 randomized trial of over 600 patients, there was no evidence of any difference in disease control (relapse-free survival of 97% on both arms), while toxicity was less for patients receiving 20 Gy (moderate to severe lethargy 5% vs. 20%, and inability to work 28% vs. 46%).

99. **What are the relative advantages of treating a para-aortic strip versus dogleg field for adjuvant radiation for stage I seminoma with respect to tumor control and toxicity (based on the best available randomized evidence)?**

On the MRC TE10 randomized trial of over 475 patients, there was no significant difference in 3-year disease-free (96.6% for dogleg vs. 96.0% for PA strip) or overall survival (100% vs. 99.3%), although there were four pelvic failures in the PA strip alone group. The PA strip patients did experience less toxicity (lower rates of nausea and vomiting, diarrhea, leukopenia, and azoospermia) compared to patients in the dogleg arm.


100. **The MRC TE19 study randomized patients with stage I seminoma to one cycle of adjuvant carboplatin (AUC 7) versus adjuvant radiation. What were the results, and does carboplatin dose matter?**

MRC TE19 found that one cycle of carboplatin is noninferior to adjuvant radiation, with 5-year RFS of 94.7% versus 96%. Though there are no randomized comparisons of carboplatin dose, patients that received two cycles appear to have slightly lower relapse risk than a single cycle, particularly if 400 mg/m² is delivered rather than AUC 7.


101. **What is the standard of care for management of stage I seminoma?**

Per NCCN, the preferred option is observation. Other options include single-agent carboplatin or RT to 20 Gy.


102. **What is the standard of care for management of stage IIA or IIB seminoma?**

The standard of care for stage IIA seminoma is radiation to a dogleg field (PA strip is not appropriate for stage II disease as these patients were excluded from the Fossa trial) to a dose of 20 Gy with a boost to
involved nodes to 30 Gy. An alternative is adjuvant chemotherapy with BEP for three cycles or EP for four cycles.

For stage IIB seminomas, options include primary chemotherapy (preferred) with BEP for three cycles or EP for four cycles. An alternative is radiation to a dogleg field to a dose of 20 Gy with a boost to 36 Gy (typically reserved for nodes 3 cm or smaller).


103. What is the standard of care for management of stage IIC or higher seminoma, or nonseminomatous germ cell tumors?

The standard of care for management of stage IIC or higher seminoma, or nonseminomatous germ cell tumors, is chemotherapy with BEP (bleomycin, etoposide, and cisplatinum). Both advanced seminomatous tumors as well as nonseminomatous germ cell tumors are radiation responsive, and infield recurrence rates are low with radiation, however, distant failure rates are high without systemic therapy in these patients.


104. What is the rate of second malignancies in long-term survivors of seminoma treated with radiation, chemotherapy, or both?

Elevated risk documented in 10-year survivors and remains above baseline for 35 years.

- Radiation: Relative risk = 2.0, 36% incidence (23% general population)
- Chemotherapy: Relative risk = 1.8, 31% incidence (23% general population)
- Both: Relative risk = 2.9


105. How would you handle radiation for a patient with trans-scrotal orchiectomy, or trans-scrotal biopsy?

Classically the inguinal nodes and scrotum were often covered in treatment fields for these patients, however, this dramatically increases contralateral testicular dose and a Royal Marsden/Princess Margaret series also describes 15% of patients having had scrotal violation without any
patient suffering scrotal or inguinal recurrence. Recommend treatment of scrotum + inguinals for gross tumor spillage with scrotal violation, or primary invasion of the scrotum by tumor.


106. When would you cover the inguinal scar?

Only for gross tumor spillage during surgery. At Cleveland Clinic, we encourage the scar to be wired for all cases as a double check on laterality of surgery/radiation.


107. What is the role of prophylactic mediastinal irradiation?

There is no longer a role as the increased risk of cardiac death exceeds any potential benefit.


108. Treatment options for a patient with a horseshoe kidney, difficulty-sparing kidney, or inflammatory bowel disease?

These patients should be treated with observation (if stage I) or chemotherapy (one to two cycles of carboplatinum for stage I patients, or BEP for stage II patients).


109. How are seminoma radiation fields set based on bony anatomy? Based on vascular anatomy?

PA strip fields are typically drawn starting superiorly at the T11-T12 interface down to L5-S1, and laterally to the tips of the transverse processes. If drawing based on vascular anatomy, contour IVC and aorta starting superiorly 2 cm below the top of the kidney and inferiorly to the bifurcation. Expand IVC by 1.2 cm and aorta 1.9 cm to create a CTV.

Dogleg fields are typically drawn starting superiorly at T11-T12 down to the top of the acetabulum. The median and lateral borders are created using lines drawn from the ipsilateral and contralateral transverse process of the 5th lumbar vertebrae down to the acetabulum. If drawing based on vascular anatomy, contour IVC and aorta starting superiorly
2 cm below the top of the kidney and inferiorly to the bifurcation, then contour ipsilateral common, external, and internal iliac vessels to the level of the acetabulum. Expand the aorta by 1.9 cm and the IVC/iliac vessels by 1.2 cm to create CTV.