ARRO-Case
Postoperative Radiotherapy in Prostate Cancer

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Case: HPI

64 year old man with ↑PSA (1.1 in 2007 → 9.0 in 2013). Asymptomatic aside from nocturia once per night. Normal GI/GU ROS, no erectile dysfunction

- ROS, PMHx, PSHx, Meds: unremarkable.
- FHx: No family history of cancers
- SHx: Married, artist, no tobacco/ETOH/drugs, 2 kids
- Physical exam: external genitalia normal, DRE reveals good tone, no blood, small prostate without nodule

Case: TRUS Biopsy

- 12 core biopsy
- Right lower: adenocarcinoma, GS 7= 4+3 in 2/2 cores
- Right upper: no pathologic abnormality
- Left lower: no pathologic abnormality
- Left upper: no pathologic abnormality

- cT1cNxMx, initial PSA 9, GS 7= 4+3
- AJCC Group IIA
- NCCN Intermediate Risk

GS = Gleason Score

AJCC Staging[1]

Primary Tumor

T1 – clinically unapparent by palpation or imaging

- T1a: incidental histologic finding in ≤ 5% tissue resected
- T1b: incidental histologic finding in > 5% tissue resected
- T1c: identified by needle biopsy

T2 – Tumor confined to within prostate

- T2a: unilateral, involves ≤ one-half of one lobe
- T2b: unilateral, involves > one-half of one lobe
- T2c: bilateral, involves both lobes

T3 – Tumor extends through prostate capsule

- T3a: extracapsular extension (EPE)
- T3b: seminal vesicle invasion (SVI)

T4 – Tumor fixed or invades other structures (eg. Bladder, rectum, pelvic wall)

Per AJCC, clinical stage may be diagnosed by DRE (digital rectal exam) or imaging (such as MRI). For research purposes, specify the T stage by DRE only or by DRE and imaging.

Regional Lymph Nodes

Nx – lymph nodes not assessed

N0 – no regional lymph node metastasis

N1 – metastasis in regional lymph nodes*

Distant Metastases

Mx – metastatic disease not assessed

M0 – no distant metastasis

M1 – distant metastasis

- M1a: non-regional lymph nodes**
- M1b: bone
- M1c: other sites with or without bone disease

**Regional lymph nodes: pelvic, hypogastric, obturator, iliac (internal, external), sacral*

***Non-regional lymph nodes: aortic, common iliac, inguinal (deep), inguinal (superficial, femoral), supraclavicular, cervical, scalene, retroperitoneal*

AJCC Grouping

- *Group I:*
  - T1a-c, PSA < 10, G ≤ 6
  - T2a, PSA < 10, G ≤ 6
  - T1-2a, PSA X, G X
- *Group IIA*
  - T1a-c, PSA < 20, G = 7
  - T1a-c, PSA 10-19, G ≤ 6
  - T2a, PSA < 20, G ≤ 7
  - T2b, PSA X, G X
- *Group IIB*
  - T2c, any PSA, any G
  - T1-2, PSA ≥ 20, any G
  - T1-2, any PSA, G ≥ 8
- *Group III*
  - T3a-b, any PSA, any G
- *Group IV*
  - any T4
  - any N1
  - any M1

** When either PSA or Gleason is unavailable, grouping should be determined by T stage and or PSA/Gleason as available.*

NCCN Risk Groups[2]

- *Very low:*
  T1c, G ≤ 6, PSA < 10, < 3 core biopsies positive
  ≤50% cancer in each core, PSA density ≤0.15ng/mL/g
- *Low:*
  T1-T2a, G ≤ 6, PSA < 10
- *Intermediate:*
  T2b-T2c, G = 7, PSA 10-20
- *High:*
  T3a, G 8-10, PSA > 20
- *Locally Advanced:*
  T3b – T4
- *Metastatic:*
  Any N1 or any M1

Treatment options for intermediate risk[2]

- For expected survival >10 years
  - Radical prostatectomy (RP) + nodal dissection
  - EBRT +/- short term ADT +/- brachytherapy
  - Brachytherapy alone

- The patient went on to receive a radical prostatectomy and nodal dissection

Case: Radical Prostatectomy

- *Prostate:* Gleason 7=4+3 prostatic adenocarcinoma involving 15% of prostate, 1cm dominant, focal **EPE at apical margin (positive margin)**, no seminal vesicle invasion, no lymph vascular space invasion
- *Bilateral iliac lymph nodes:* **3 benign nodes**

- pT3aN0 Mx with + apical margin
- AJCC Group III
- NCCN High risk

Adverse Pathologic Features

- Factors predicting biochemical recurrence[3-7]:
    1. pT3a (EPE)*
    2. pT3b (SVI)*
    3. Positive margin*
    4. Detectable postoperative PSA*
    5. Gleason 8-10*
    6. Nodal involvement
    7. High pre-operative PSA
    8. PSA-DT < = 10 months and, especially, < 3 months
    9. PSA Velocity > 2ng/mL/year

*NCCN adverse features

Adverse Pathologic Features

- Highest risk of recurrence:
    1. Seminal vesicle invasion (SVI)[11]
    2. Extra-prostatic extension (EPE) [11]
    3. Positive surgical margins[11]
    4. Detectable postoperative PSA[9]
    5. Gleason 8-10[9]

Post-RP Options (NCCN)

1. Adjuvant radiation therapy (ART)

2. Observation with salvage radiation therapy (SRT) if needed

Post-RP Options

1. ART – before recurrence
   - Immediate post-operative
   - Allows for potential overtreatment

2. SRT – after recurrence
   - Serial monitoring of PSA and select SRT for PSA failure
   - Risk of PSA rising rapidly and compromising effectiveness of RT
   - For high grade tumors, may risk metastasis due to delay in therapy[12]

ART or Observation?

- 15-60% of patients develop PSA failure after RP
- Rising PSA after RP:
  - 1/3 will develop DM at median of 8 years
  - 17% will die of prostate cancer within 15 years
- However, ART risks ↑toxicity and ↑cost
- Can upfront post-operative RT reduce distant failure?

Evidence for ART

	SWOG 8794	EORTC 22911	ARO 96-02
Inclusion	Post-RP pT3N0 or +margin	Post-RP pT2-3N0 with extra-capsular disease (+margin, ECE, SVI)	Post-RP pT3N0 or +margin randomized prior to post-op PSA
Randomization Arms	60-64Gy vs observation	60Gy vs observation	60Gy vs observation
Follow-Up interval	15 years	10 years	10 years
Results	**RT improved DMFS (43% v 54%) *** RT improved LRF (8% v 22%) RT improved OS (74% v 66%) RT improved clinical progression-free survival	**RT improved bPFS (61% v 41%)*** RT improved LRR (7 % v 17%) No difference in DM, OS, or CSS RT improved clinical progression-free survival	**RT improved bPFS (56% v 35%)*** No significant difference in DMFS or OS (not powered to detect these differences)
Toxicity	GU symptoms and Global QoL initially worse with RT, but no difference at 5 years RT arm higher: urethral stricture, total incontinence, proctitis	Acute: Grade 2 (20%), Grade 3 (≤5%) Late: Grade 2 (10%), Grade 3 (≤2%)	Acute: Grade 2 (12%), Grade 3 (3%) Late: Grade 2 (5%), Grade 3 (1%)

*primary end-point

ART Summary

- If adverse risk factors are present, then adjuvant RT reduces the risk of:
  - biochemical recurrence
  - local recurrence
  - clinical progression of cancer
  - improves OS and distant mets

- If any adverse risk factors are present (see slide 11), ART should be offered as an option[13,14]

Evidence for SRT

	Trock *et al* JAMA 2008	Boorjian *et al* Journal of Urology 2009	Stephenson *et al* Journal of Clinical Oncology 2007
Patients	Post-RP Median PSA ~0.8	Post-RP Biochemical recurrence Median PSA ~ 0.8	Post-RP Median PSA 1.1 51% margin+, 22% GS 8+, 3% N1
Treatment	SRT v observation Median RT dose 66.5 Gy 12% received SRT + ADT	SRT v observation 32% received SRT	SRT all Median RT dose 64.8 Gy 14% received SRT + ADT
Results	RT improved prostate-cancer specific survival (85% v 62%)	RT decreased local recurrence (~90%) RT decreased risk of systemic progression (~75%) RT decreased late-ADT(~20%)	6 year progression-free probability 32% If PSA </= 0.5 at time of SRT: 6 year FFP 48% If PSA > 0.5 at time of SRT: 6 year FFP 26%

SRT Summary

- Consider re-staging evaluation in patient with PSA failure
  - i.e. Bone Scan and MRI Pelvis
  - Identify local recurrence v. metastatic disease
- SRT should be offered for local recurrence with no DMs[2]
- SRT is most effective when pre-RT PSA is low

  - </= 0.4ng/mL or at least </= 1.0ng/mL [15,16]
- If limited life expectancy or slow PSA rise, SRT may have limited benefit survival benefit over ADT or observation

Adjuvant RT? or Salvage RT?

- SRT exposes less patients to RT than an ART approach
- SRT may allow for disease progression
- The option of SRT potentially limits:
  - Toxicity (acute and late GU, GI, and sexual)
  - Cost

- Ongoing clinical trials to evaluate ART v SRT:
  - RADICALS
  - RAVES

Case: Postoperative course

- **Post-op PSA <0.02, patient chose observation**
- Patient's PSA trend:

Time since RP	3mo	6mo	12mo	15mo	18mo
PSA (ng/mL)	0.02	0.02	0.02	0.12	0.16

- Re-staging CT Abdomen & Pelvis and Bone Scan: no evidence of disease

Post-RP PSA failure[3, 9]

- PSA levels post-RP should be undetectable
- Biochemical Recurrence: PSA ≥ 0.2 ng/mL confirmed by a second determination ≥ 0.2
- ½ of men with PSA doubling time > 10-12 months will die from prostate cancer in 10-13 years

Post-op RT Recommendations

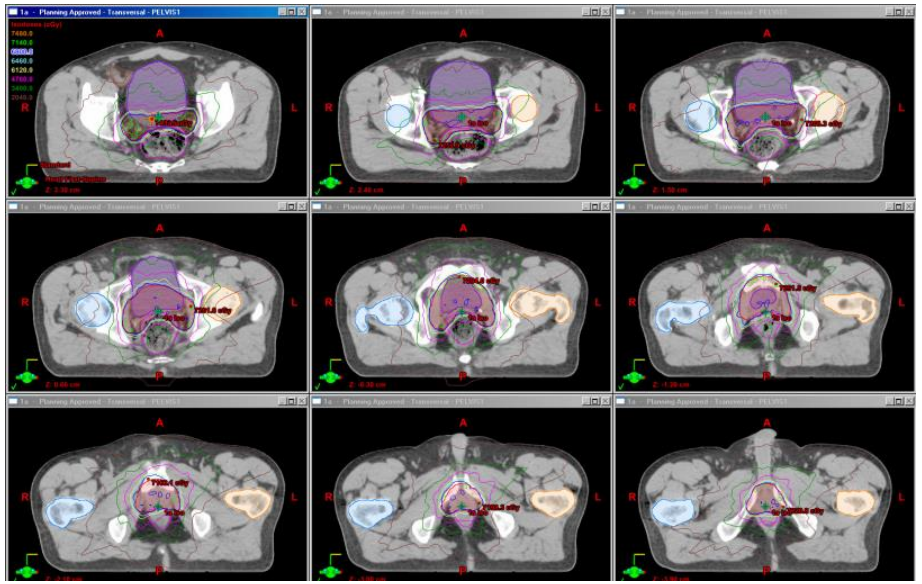
- ***Treatment volume:*** Prior trials used small-volume RT with no pelvic nodal irradiation.
  (RTOG 0534 is an ongoing post-op trial evaluating prostate bed RT alone +/-ADT versus pelvic lymph node RT + prostate bed RT + ADT)

- ***Dose:*** > 64-65 Gy per ASTRO/AUA consensus panel (NCCN: 64-72Gy), but higher dose with high PSA or nodule

Case: Radiotherapy Technique

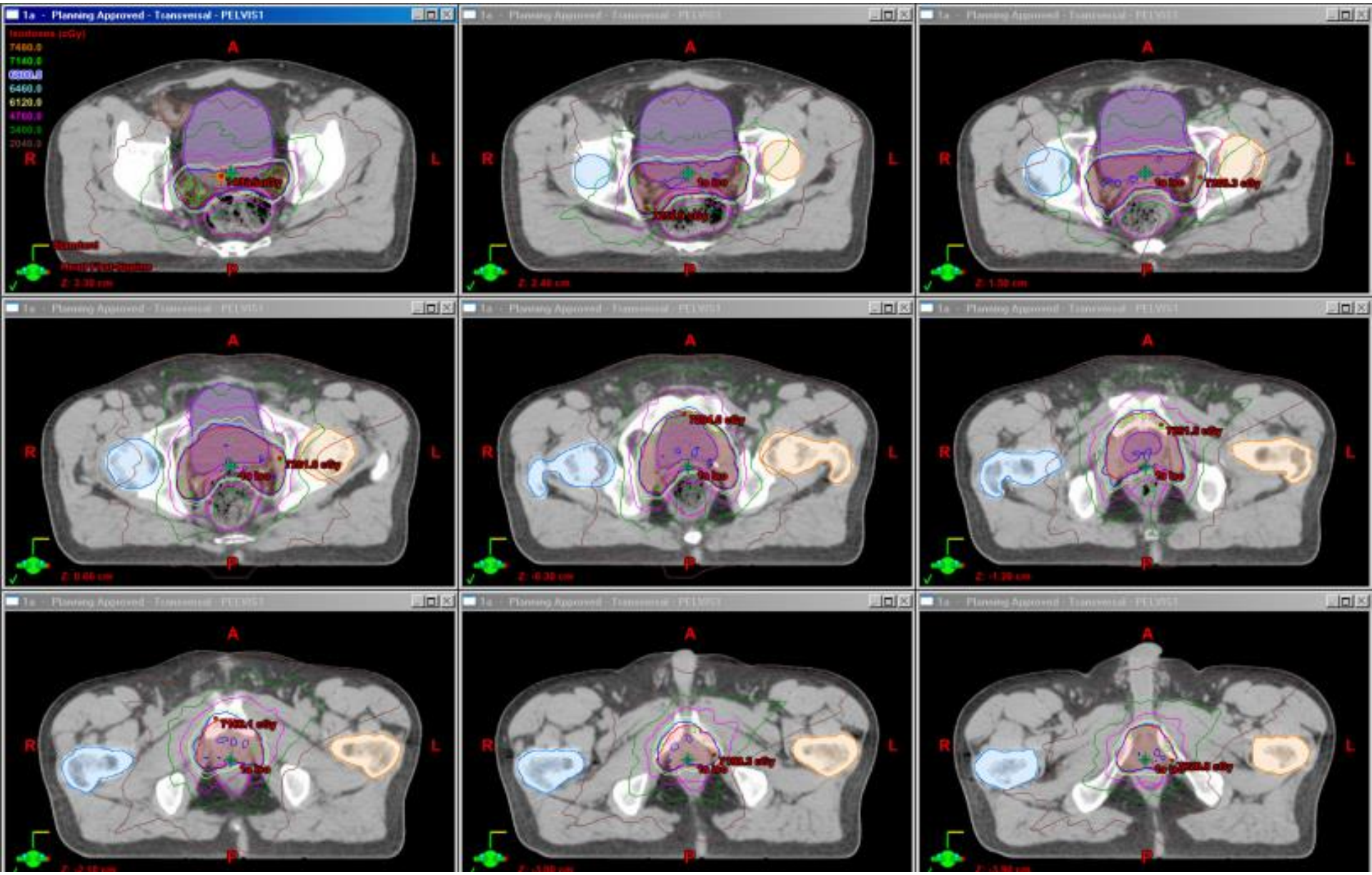
- Prostate fossa target atlas available through RTOG Contouring Atlas

- IMRT
- 68 Gy in 34 fractions



Planning Parameters (per RTOG 0534)

- Rectum
  - V65 < 35%
  - V40 < 55%
- Bladder (bladder minus CTV)
  - V65 < 50%
  - V40 < 70%
- Femoral Heads
  - V50 < 10%


1a - Planning Approved - Transversal - PELVIS1
Isodoses (cGy)
7480.0
7140.0
6800.0
6460.0
6120.0
A
R
L
P

Selection | Registration | Contouring | Field Setup | Plan Evaluation

Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		bladder	Approved	1a	C1	262.9	100.0	100.0	411.4	7434.6	4328.0
☑		penile bulb	Approved	1a	C1	2.6	100.0	100.2	6764.3	7239.0	6966.4
☑		PTV	Approved	1a	C1	268.1	100.0	100.0	4986.0	7434.6	6955.8
☑		rectum	Approved	1a	C1	186.1	100.0	100.0	290.8	7180.2	2836.8
☑		bowel	Approved	1a	C1	588.4	100.0	100.0	31.5	2425.0	186.7
☑		bowel kjf	Approved	1a	C1	252.5	100.0	100.0	137.3	4316.8	530.1
☑		femur L	Approved	1a	C1	135.5	100.0	100.0	359.4	4897.6	1568.9
☑		femur R	Approved	1a	C1	131.4	100.0	100.0	578.7	4047.8	1771.3
☐		External	Approved	1a	C1						
☐		CT MARK	Approved	1a	C1						

Case: Toxicity & Follow up

- PSA: undetectable
- Grade II diarrhea improved with Carafate enemas and Imodium. 3 day treatment break due to this toxicity.
- 1 month follow up:

  Grade I urinary leakage and frequency
- 6 month follow up:

  Erectile Dysfunction – effectively treated with Tadalafil (Cialis)
- 1 year follow up:

  Nocturia: x 2 per night

  Urinary leakage/frequency: resolved

  ED: stable

What about ADT?

- The data to support ADT + ART or SRT post-RP is still unclear

- Clinical Trials to evaluate this question:

  RTOG 9601 – DFS advantage with 2 years of Bicalutamide[16]

  RTOG 0534 (SPPORT protocol) – open, to determine the advantage of ADT + post-op RT

What about ADT?

- If very unfavorable risk factors, it is reasonable to recommend ADT

- Logistics to consider:
  - ADT may obscure interpretation of PSA response
  - Significant side effects

    RTOG 9601 with Bicalutamide: gynecomastia

    RTOG 0534 with Lupron/Biclutamide: weight gain, hot flashes, hyperglycemia, fatigue

ASTRO/AUA
Key Recommendations

Please see the following recently published paper for Key Recommendations for Adjuvant and Salvage Radiotherapy After Prostatectomy:

Valicenti RK, Thompson I, Albertsen P, et al. Adjuvant and Salvage Radiation Therapy After Prostatecomy: American Society for Radiation Oncology/American Urological Association Guidelines. Int J Radiation Oncol Biop Phys, 2013. 86 (5): 822-828.

Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and Salvage Radiotherapy After Prostatecomy: AUA/ASTRO Guidelines. The Journal of Urology 2013. 190 (2): 441 – 449.

RTOG Contouring Atlas

http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx

References

1. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging manual. New York, NY: Springer; 2010.
2. Prostate Cancer Version 1.2015. 2015. at http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.)
3. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 2004;351:125-35.
4. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J Urol 2004;172:S42-6; discussion S6-7.
5. Grossfeld GD, Tigrani VS, Nudell D, et al. Management of a positive surgical margin after radical prostatectomy: decision analysis. J Urol 2000;164:93-9; discussion 100.
6. D'Amico AV, Whittington R, Malkowicz SB, et al. The combination of preoperative prostate specific antigen and postoperative pathological findings to predict prostate specific antigen outcome in clinically localized prostate cancer. J Urol 1998;160:2096-101.
7. Lowe BA, Lieberman SF. Disease recurrence and progression in untreated pathologic stage T3 prostate cancer: selecting the patient for adjuvant therapy. J Urol 1997;158:1452-6.
8. Morgan SC, Waldron TS, Eapen L, Mayhew LA, Winquist E, Lukka H. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: a systematic review and meta-analysis. Radiother Oncol 2008;88:1-9.
9. Freedland SJ, Rumble RB, Finelli A, et al. Adjuvant and Salvage Radiotherapy After Prostatectomy: American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol 2014.
10. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant Radiotherapy Versus Wait-and-See After Radical Prostatectomy: 10-year Follow-up of the ARO 96-02/AUO AP 09/95 Trial. Eur Urol 2014;66:243-50.
11. Swanson GP, Riggs M, Hermans M. Pathologic findings at radical prostatectomy: risk factors for failure and death. Urologic Oncology 25 (2007) 110 – 114.
12. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. International journal of radiation oncology, biology, physics 2014;89:1038-46.
13. Valicenti RK, Thompson I, Jr., Albertsen P, et al. Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. Int J Radiat Oncol Biol Phys 2013;86:822-8.
14. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 2013;190:441-9.
15. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol 2006;24:3973-8.
16. ASTRO Meeting abstract: Shipley WU, Hunt D, et al. Initial Report of RTOG 9601: A Phase III Trial in Prostate Cancer: Anti-androgen Therapy (AAT) with Bicalutamide during and after Radiation Therapy (RT) Improves Freedom from Progression and Reduces the Incidence of Metastatic Disease in Patients following Radical Prostatectomy (RP) with pT2-3, N0 Disease, and elevated PSA Levels. IJROBP 2010; 78 (3).
17. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007;25:2225-9.
18. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. Jama 2008;299:2760-9.