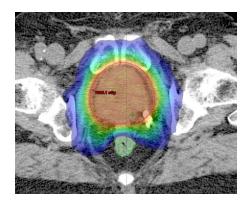
The first congress and workshop of Georgian Association of Oncological Urology October 4-5 2017

The role of radiotherapy in the management of locally advanced and metastatic prostate cancer

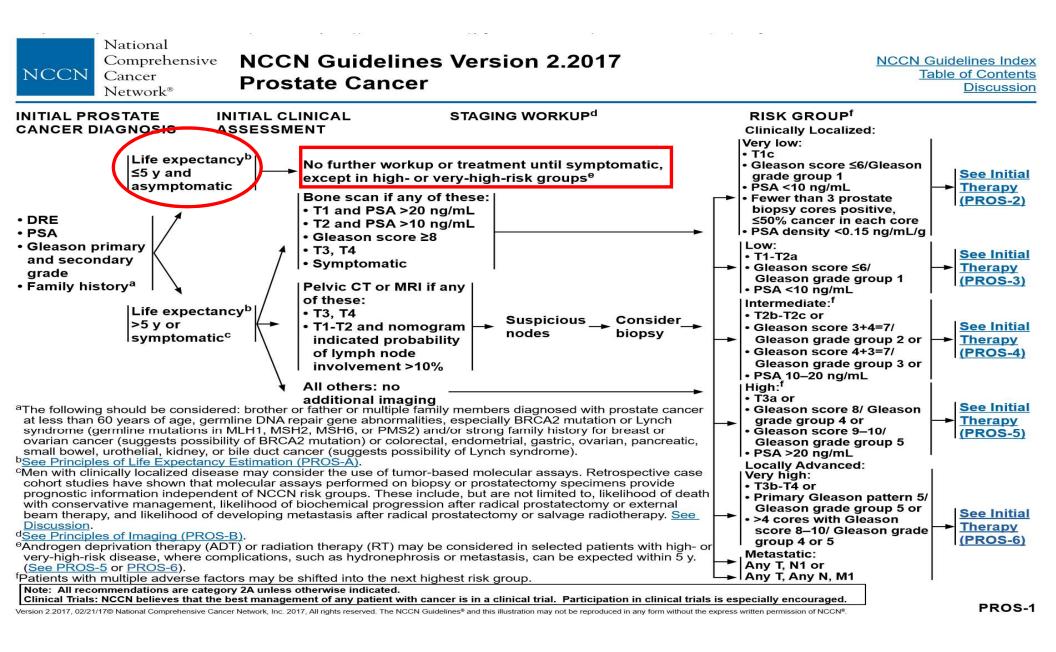


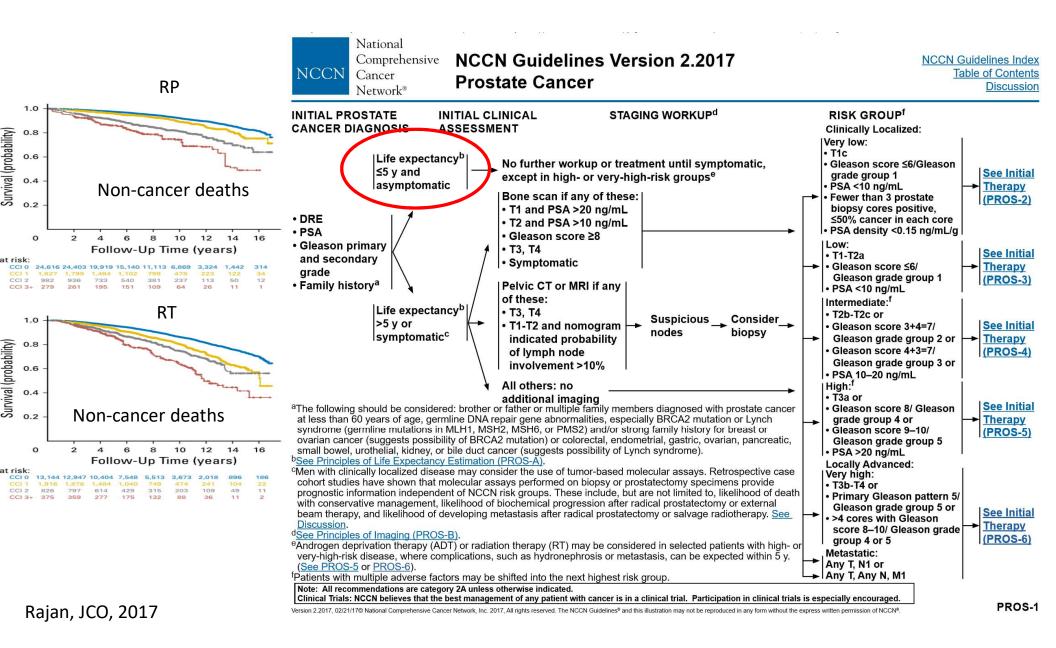


Merdan Fayda, MD Professor of Radiation Oncology <u>İSTİNYE</u> ÜNİVERSİTESİ



- Definition and diagnostic work-up
- Treatment options
- Adjuvant RT
- Curative RT
- Local radiotherapy for metastatic cases
- Radiosurgery for oligomets
- Palliative RT





ANATOMIC STAGE/PROGNOSTIC GROUPS *

Group	Т	Ν	М	PSA	Gleason
	T1a-c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA ≥10 <20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
Ш	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Very low: • T1c • Gleason score ≤6/Gleason grade group 1 • PSA <10 ng/mL • Fewer than 3 prostate

biopsy cores positive, ≤50% cancer in each core • PSA density <0.15 ng/mL/g

High:[†]

- T3a or
- Gleason score 8/ Gleason grade group 4 or
- Gleason score 9–10/ Gleason grade group 5
- PSA >20 ng/mL

Low:

- T1-T2a
- Gleason score ≤6/
 - Gleason grade group 1
- PSA <10 ng/mL

Intermediate:^f

- T2b-T2c or
- Gleason score 3+4=7/
- Gleason grade group 2 or
- Gleason score 4+3=7/
- Gleason grade group 3 or
- PSA 10–20 ng/mL

Locally Advanced: Very high:

- T3b-T4 or
- Primary Gleason pattern 5/ Gleason grade group 5 or
- >4 cores with Gleason score 8–10/ Gleason grade group 4 or 5

Table T Delinition of locally advanced or very nigh-risk PCa						
Author	Definition					
Spahn <i>et al.</i> ²²	PSA >20 + risk factor (GS 8–10 and/or cT3–4)					
Walz et al. ²¹	Multiple risk factor (PSA >20, GS 8–10, cT3–4)					
Joniau <i>et al.</i> ²³	GS 8–10 + risk factor (PSA >20 and/or cT3–4)					
Sundi <i>et al.</i> ²⁴	GS 5 or \geq 5 cores with GS 8,9 or multiple risk					
NCCN guideline ²⁰	T3b-T4					
EAU guideline ³	cT3–4 or cN ⁺					
Walz <i>et al.</i> ²¹ Joniau <i>et al.</i> ²³ Sundi <i>et al.</i> ²⁴ NCCN guideline ²⁰	Multiple risk factor (PSA >20, GS 8–10, cT3–4) GS 8–10 + risk factor (PSA >20 and/or cT3–4) GS 5 or \geq 5 cores with GS 8,9 or multiple risk T3b–T4					

Table 1 Definition of locally advanced or very high-risk PCa

Saika, IJU, 2017

Prostate cancer at first diagnosis

- Local disease 80%
- Regional disease 12 %
- Metastatic 8 %

5y survival ~ 100% 5y survival ~ 100 %

5y survival ~ 30 %

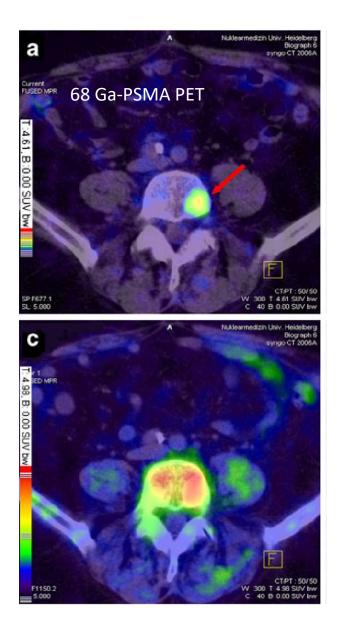
ACS, website

Diagnostic work-up

• Bone scan



- Bone scan is indicated in the initial evaluation of patients at high risk for skeletal metastases.
 - ► T1 disease and PSA ≥20, T2 disease and PSA ≥10, Gleason score ≥8, or T3/T4 disease
 - Any stage disease with symptoms suggestive of osseous metastatic disease



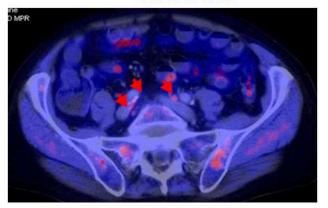
68Ga-PSMA PET/CT for recurrence

 (68)Ga-PSMA PET/CT can detect lesions characteristic for PC with improved contrast when compared to standard (18)Ffluoromethylcholine PET/CT, especially at low PSA levels for recurrent prostate cancer.

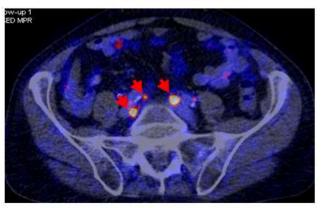
Afshar-Oromieh, EJNMMI, 2014

Lymph nodes

¹¹C-choline



68Ga-PSMA



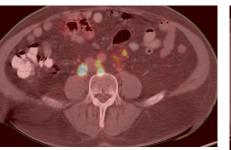
68 Ga PET Primary cancer staging

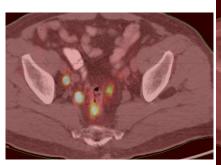
 68 Ga PET has higher detection rate for lymph node and bone lesions

Schwenck, ENMMI, 2017

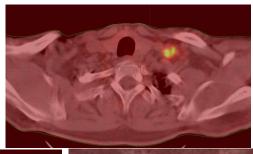
Primary staging- 68Ga-PSMA PET

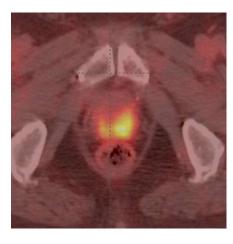
Prostate cancer











PSMA after Hormonotherapy



RT vs surgery in high risk disease



- No randomized comparison
- Retrospective pooled analysis showed that RT has worse PCSM than surgery
 - aHR = 2.08 (1.76-2.47) p<0.000001
 - More favorable and healthy people could go to surgery
 - Hormontherapy may not be optimal
 - Lower doses than the standard döşe
 - If you correct these errors the 10 year CSS difference between RP and RT would be less than 1%

Roach III, IJROBP, 2015 Wallis, EU, 2016

Table 4 Oncological outcomes of RALP for locally advanced PCa										
Authors	n	Very high-risk criteria	Mean/median preoperative PSA	Stage ≥pT3 (%)	PSM (%)	BCR criteria	BCR (%)	BCRFS time estimate, % (years)	Mean follow up in months	
Ham <i>et al.</i> ³⁵	121	≥cT3	65.8	96	48.8	NI	NI	NI	NI	
Casey et al. ³⁶	35	≥pT3	7	100	20	NI	28.6	NI	13.3	
Vora et al. ³⁷	140	≥pT3	8.3	100	47.1	PSA >0.2	18.5	50.0 – 1 year	54	
Koo et al. ³⁸	53	≥cT3b or cN1	26.3	NI	60	PSA >0.2	NI	20.0 – 2 years	36.1	
Gandaglia <i>et al.</i> ³⁹	94	≥cT3	9.7	76.6	32.3	PSA >0.2	22.3	63.3 – 3 years	23.5	

NCCN Guidelines Version 2.2017 Comprehensive **NCCN Guidelines Index** NCCN **Table of Contents** Cancer **Prostate Cancer** Discussion Network[®] Adverse features: **RISK GROUP INITIAL THERAPY** ADJUVANT THERAPY Detectable PSA EBRTⁱ + ADT^m (2–3 y; category 1)^q Margin positivity Extra capsular extension See Monitoring (PROS-7) or Seminal vesicule infiltr. Adverse feature(s) and no EBRTⁱ + brachytherapy ± ADT^m Undetectable PSA See Monitoring Very high: lymph node metastases:^k (2-3 y) after RP or PSA (PROS-7) • T3b-T4 or EBRTⁱ nadir after RT Primary Gleason or pattern 5/ Observation¹ Gleason grade or group 5 No adverse features or lymph or RP^j + PLND (in select patients)^r >4 cores with node metastases See Radical Gleason score Prostatectomy 8–10/ Gleason

Lymph node metastasis:

See Monitoring (PROS-7)

See Monitoring (PROS-7)

(category 2B)

Observation

or

ADT^m (category 1) ± EBRTⁱ

Biochemical Failure

See Radiation Therapy

Recurrence (PROS-9)

(PROS-8)

or

PSA failure

National

grade group 4

or 5

Regional:

Any T, N1, M0

Metastatic: Any T,

Any N, M1

or

or ADT^m

► ADT^m

ADT^m or observation for patients

EBRTⁱ + ADT^m (2–3 y; category 1)

who are not candidates for

definitive therapy

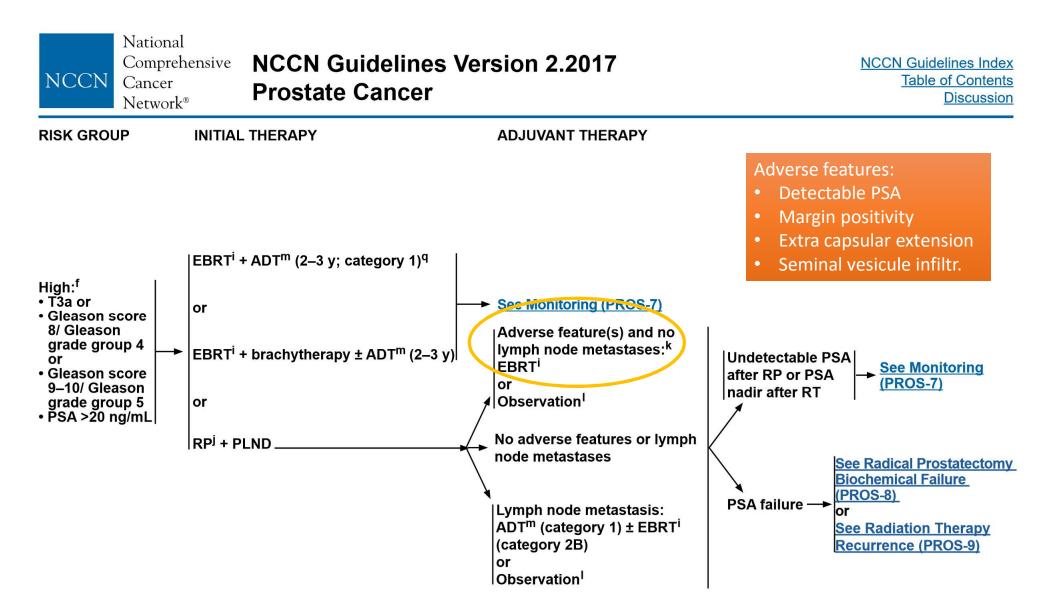


Table 1 Randomized Clinical Trials of Postoperative Radiation vs Observation After Radical Prostatectomy With Adverse	Pathologic Features
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Trial	Enrollment Dates	Median f⁄u	Arms	n	Risk Factors	% Receiving assigned Rx	RT Timing, Dose, and Technique	Neoadj ADT (Before RP)	Definition of PSA Progression	bPFS	cPFS	MFS	OS	Salvage Tx
SWOG 8794	8/1988-1/1997	12.7 у	Adjuvant radiation	214	ECE or R1: 67% SVI: 10% pN0: 100% GS 7-10: 43% Prooperative PSA level ≥ 10 ng/mL: 53% Postoperative PSA level	95%	≤ 18 wk post-op 60Gy/30 fs-64Gy/32 fx RT: conventional Tx Vol: PF and periprostatic tissue	9%	> 0.4 ng/mL	10 y: ~50% Median: 10.3 years	Median: 13.8 years	,	10 y: 74% Median: 15.2 y	Salvage HT by year 5: 10%
		12.5 y	Observation	211	≥ 0.2 ng/mL: 35% ECE or R1: 67% SVI: 11% PN0: 100% GS 7-10: 54% Preoperative PSA level ≥ 10 ng/mL: 48% Postoperative PSA level ≥ 0.2 ng/mL: 32%	98%	_	8%		10 y: ~25% Median: 3.1 y	Median: 9.9 y	10 y: 61% Median: 12.9 y	10 y: 66% Median: 13.3 y	Salvage RT: 33 Salvage HT by year 5: 21%
EORTC 22911	11/1992- 12/2001	10.6 years	Adjuvant radiation	502	ECE: 75% R1: 62%	82%	Median 90 d post-op 60 Gy/30 fx	10%	> 0.2 ng/mL above post-RP value	5 y: 74.0%	10 y: 70.3%	10 y: 76.5%	5 y: 93.1%	Salvage HT by year 5: 10.1%
	122001		Inclusion		SVI: 25% pN0: 98.6%		4 field (70%) Tx Vol:		pos-ru talue	10 y: 60.6%			10 y: 76.9%	year 5. 10.1 x
					WHO 2-3: 85% Preoperative PSA level: median 12.3 ng/mL Postoperative PSA level > 0.2 ng/mL 9.2%		Large field (>9 × 9 cm eqsq) in 92.3% Small field (<9 × 9 cm eqsq) in 54.0%			Median: 6.12 y				
		10.6 y	Observation	503		98%	_	10%		5 y: 52.6% 10 y: 41.1% Median: 13.2 y	10 y: 64.8%	10 y: 71.3%	5 y: 92.3%;	Salvage RT: 33%
					pN0: 99.6% WHO 2-3: 88% Preoperative PSA level: median 12.4 ng/mL Postoperative PSA level > 0.2 ng/mL: 12.3%					Median: 15.2 y			10 y: 80.7%	Salvage HT by year 5: 15.5%
ARO 96-02	4/1997-9/2004 (required	9.3 y	Adjuvant radiation	148	R1: 68%	77%	Median 81 days postoperation 60 Gy/30 fx	11%	2 Consecutive PSA level increases	5 y: 72% 10 y: 56%	NR	NR	NR	NR
	undetectable post-op PSA)				SVI: 27% pN0: 98.6% GS 7-10: 62% Preoperative PSA level: median 9.7 ng/mL Postoperative PSA level:		3 or 4 field, 3D-CRT Tx Vol: Surgical margins (apex to SV) + 1 cm			Median: NR				
		9.4 y	Observation	159	R1: 61%	97%	-	12%		5 y: 54% 10 y: 5%	NR	NR	NR	NR
					SVI: 27% pNO: 98.1% GS 7-10: 64% Preoperative PSA level: median 9.4 ng/mL Postoperative PSA level: < 0.1 ng/mL					Median: 5.5 y				

Abbreviations: CRT, conformal radiation therapy; ECE, extracapsular extension; f/u, follow-up; fx, fraction; GS, Gleason score; NR, not reported; SV, seminal vesicle; Tx, treatment; Vol, volume.

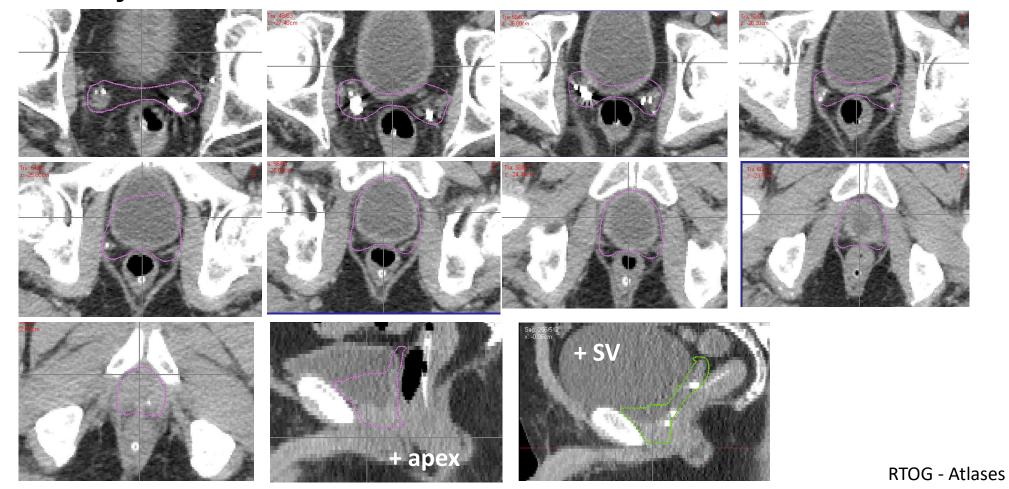


Table 1Acute toxicity effects of RT after prostatectomy(ranges based on RTOG or CTCAE grading system)

Study	Genitou	irinary	inary Gastroin		
arm type	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4	
Adjuvant	10.5%-26%	2.0%-8.0%	22.0%-25.0%	0.0%-2.0%	
Salvage	3.0%-82.0%			0.0%-2.2%	
Mixed	5.0%-92.0%	0.0%-3.0%	4.3%-87.0%	0.0%-1.3%	

Valicenti, IJROBP, 2013

Table 2Late toxicity effects of RT after prostatectomy(ranges based on RTOG/EORTC or CTCAE grading system)

Study	Genito	urinary	inary Gastrointestinal		
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4	
Adjuvant	2.0%-22.0%	0.0%-10.6%	1.0%-12.7%	0.0%-6.7%	
Salvage	1.0%-49.0%	0.0%-6.0%	0.0%-66.0%	0.0%-18.0%	
Mixed	1.3%-79.0%	0.0%-17.0%	2.0%-59.0%	0.0%-4.3%	

Valicenti, IJROBP, 2013

Conclusions: Physicians should offer adjuvant radiation therapy to patients with adverse pathologic findings at prostatectomy (ie, seminal vesicle invastion, positive surgical margins, extraprostatic extension) and salvage radiation therapy to patients with

prostate-specific antigen (PSA) or local recurrence after prostatectomy in whom there is no evidence of distant metastatic disease. The offer of radiation therapy should be made in the context of a thoughtful discussion of possible short- and long-term side effects of radiation therapy as well as the potential benefits of preventing recurrence. The decision to administer radiation therapy should be made by the patient and the multidisciplinary treatment team with full consideration of the patient's history, values, preferences, quality of life, and functional status. The American Society for Radiation Oncology and American Urological Association websites show this guideline in its entirety, including the full literature review. © 2013 Elsevier Inc.

Valicenti, IJROBP, 2013

Salvage RT

- Detectable PSA after surgery
- N=2460
- Med FU 5 years
- 5year FFBF
 - 71% for PSA 0.01-0.2
 - 37% for PSA >2 ng/mL

Node positive disease



NCCN, 2017

Curative raditoherapy for node positive

Study	Study Design	Median Follow-Up (Y)	No. of Patients	Overall Survival	Prostate Cancer– Specific Survival	Recurrence-Free Survival
Definitive radiother	rapy (RT) vs no RT					
Zagars et al ⁵	Retrospective, single institution	ADT: 9.4 RT+ADT: 6.2	255	(10 y) ADT: 46% RT + ADT: 67% (<i>P</i> = 0.008)	N/A	(10 y) ADT: 25% RT + ADT: 80% (P < 0.001)
Lin et al ⁶	Retrospective, National Cancer Data Base	2.7	638	(5 y) ADT: 53% RT + ADT: 72% (<i>P</i> < 0.001)	N/A	N/A
Tward et al ⁷	Retrospective, SEER	7.5	1100	(5 y) No RT: 56% RT: 68% (P < 0.01)	(5 y) No RT: 71% RT: 78% (P < 0.01)	N/A
Rusthoven et al ⁸	Retrospective, SEER	6.8	2991	(10 y) RT: HR = 0.57 (<i>P</i> < 0.001)	(10 y) RT: HR = 0.58 (P < 0.001)	N/A
Radiotherapy (RT)	alone vs RT plus ADT					
RTOG 85-31 ^{10,11}	Secondary analysis of randomized trial data	6.5	173	(5 y) RT: 62% RT + ADT: 72% (multivariate <i>P</i> = 0.03)	Favors RT + ADT (Percentages not reported; multivariate $P = 0.014$)	(5 y) RT: 10% RT + ADT: 54% (multivariate <i>P</i> < 0.001)
Granfors et al ¹²	Secondary analysis of randomized trial data	9.7	39	Favors $RT + ADT$ ($P = 0.005$)	N/A	N/A

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; N/A, not available; PFS, progression-free survival; RTOG, Radiation Therapy Oncology Group; SEER, Surveillance Epidemiology & End Results.

Broughman, SRO 2016

Postop RT for node positivity

Table 3 Studies Evaluating Radical Prostatectomy and Adjuvant Treatments for Node-Positive Prostate Cancer

Study	Study Design	Median Follow-Up (Years)	No. of Patients	Overall Survival	Prostate Cancer–Specific Survival	Recurrence-Free Survival
Radical prosta	tectomy (RP) vs conservative man	nagement				
Frohmüller et al ⁴⁹	Retrospective, single institution	ADT: 4.7 ADT + RP: 4.3	139	(10 y) ADT: 30% RP + ADT: 51% (<i>P</i> = 0.067)	(10 y) ADT: 32% RP + ADT: 71% (<i>P</i> = 0.002)	(10 y) ADT: 15% RP + ADT: 36% (P = 0.002)
Engel et al ¹⁶	Retrospective, Munich Cancer Registry	5.6	938	(7 – 0.007) (5 y) ADT: 60% RP + ADT: 84% (<i>P</i> value unknown)	(5 y Relative survival) ADT: 70% RP + ADT: 95% (<i>P</i> value unknown)	N/A
Steuber et al ⁵⁰	Retrospective, single institution	8.2	158	N/A	(10 y) ADT: 46% RP + ADT: 76% ($P = 0.001$)	(10 y) ADT: 31% RP + ADT: 61% (<i>P</i> = 0.005)
Adjuvant ADT	vs observation					
ECOG 3886 ^{17,18}	Randomized trial	11.9	98	(Median) Adjuvant ADT: 13.9 y Observation (delayed ADT): 11.3 y (<i>P</i> = 0.04)	(Median) Adjuvant ADT: Not reached Observation (delayed ADT): 12.3 y ($P < 0.001$)	(PFS) Favors adjuvant ADT (multivariate $HR = 4.11$ ($P < 0.001$)
Adiumant radia	therapy (RT) vs no RT					
Adjuvant radio Briganti et al ¹⁹	Retrospective, 2 institutions	7.9	364	(10 y) ADT: 55% ADT + RT: 74% (<i>P</i> < 0.001)	(10 y) ADT: 70% ADT + RT: 86% (<i>P</i> = 0.004)	N/A
Kaplan et al ²¹	Retrospective, SEER-Medicare	N/A	577	(10 y) No RT: 3.77 deaths/100 person-y RT: 5.09 deaths/100 person-y (<i>P</i> = 0.153)	(10 y) No RT: 1.31 deaths/ 100 person-y RT: 2.89 deaths/100 person-y (<i>P</i> = 0.09)	N/A

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; N/A, not available; PFS, progression-free survival.

Broughman, SRO 2016

Local radiotherapy for metastatic cancer

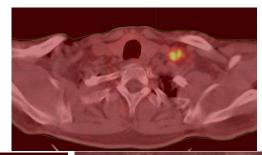
- SEER-based Culp study n=8185
 - Radical prostatectomy n=245
 - Brachytherapy n=129
 - No local tx n=7811
- Munich cancer registry
 - Radical prostatectomy n=74
 - No local tx n=1464

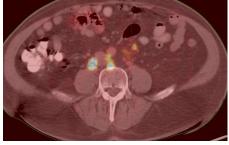
udy n=8185		No local tx	Radical prostatectomy	Brachytherapy		
my n=245	5-year OS	22.5%	67.4%	52.6%		
29	Cancer spes. survival	48.7%	75.8%	61.3%		
med.FU: 16 months						

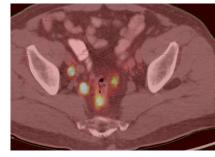
	No local tx	Radical prostatectomy
5-year OS	21%	55 %

Randomized trials are needed

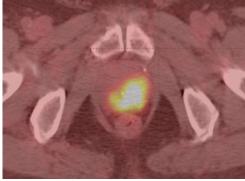
Culp, EU, 2014

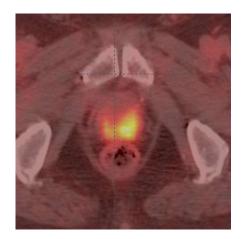




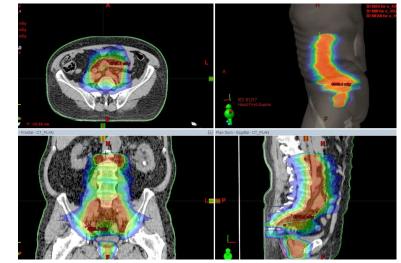








PSMA after 1y Hormonotherapy



Metastasis directed treatment for oligo mets (\leq 5)

- Rationale
 - Nonsmall cell lung cancer 5 y OS 23 % with met directed treatments
 - Colon cancer 5 y OS 50 %
 - Prostate cancer ??
 - Surgery / radiosurgery to the metastatic site or radiosurgery

Study	No. of Patients	Treatment	Median Follow-Up (Months)	Metastatic Sites Treated (Nodes/ Bone/Visceral)	Outcomes
Schick et al ⁴¹	50	IMRT	31	33/15/2	(3 y) OS: 92%; BRFS: 55%; CFFS: 59%. No grade 3 toxicity
Muacevic et al ⁴⁶	40	SBRT	14	0/40/0	(2 y) LC: 95.5%
Decaestecker et al ⁴⁷	50	SBRT	25	27/22/1	(2 y) LC: 100%; PFS: 35%. Grade 1 toxicity: 17%; Grade 2 toxicity: 6%
Berkovic et al ⁴⁸	24	SBRT	24	11/13/0	(2 y) LC: 100%; PFS: 42%. No grade 3 toxicity

Table 4 Studies Evaluating Aggressive Metastasis-Directed Treatment in Patients With Oligometastatic Prostate Cancer

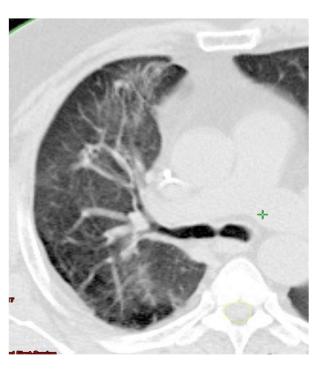
Abbreviations: BRFS, biochemical recurrence-free survival; CFFS, clinical failure-free survival; IMRT, intensity-modulated radiation therapy; LC, local

LIV HOSPITAL RMC - Treatments

Stereotactic RT SRS/SBRT



before

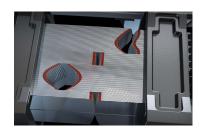




after

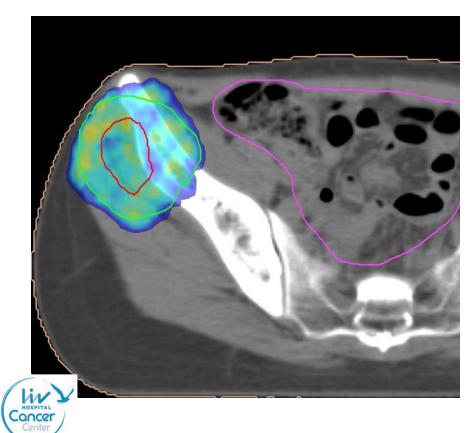
Palliative radiotherapy

30 Gy – Full Dose



Ŕ

15 Gy – Half Dose



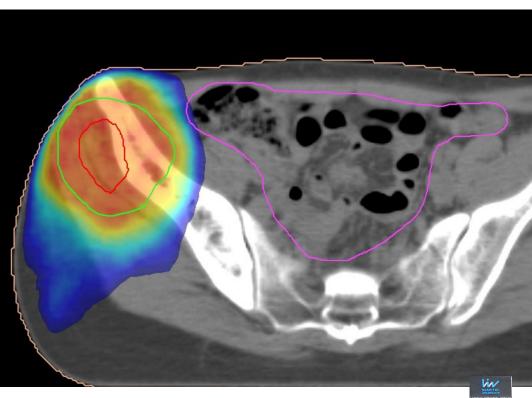
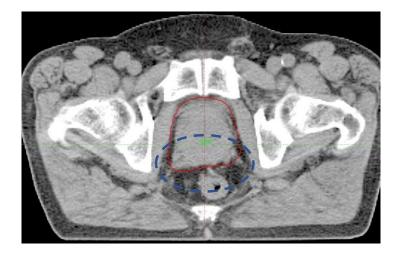
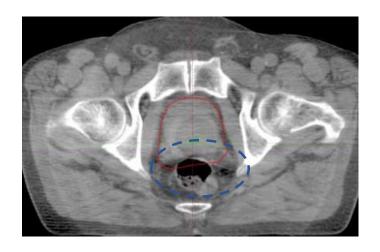
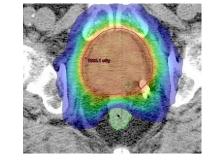


Image guided radiotherapy – IGRT

«Treat what you see, with proper positioning»







ance

Daily 3D IGRT can warn you about the little daily changes



Summary

- The 68-Ga PET-BT could identify some small lymph node (Could spare unnecessary pelvic RT).
- RP and radiotherapy are viable options in tx of locally advanced cancer
- According postop RT guideline, almost all cases would need postop Adjuvant RT and is not an innocent procedure
- The salvage RT is more effective in the case of lower PSA (i.e.<2 even smaller)

Summary-2

- Local radiotherapy could be helpful in selected cases. Without rand. data, I prefer to choose patients with good reponse to initial systemic agent
- Radiosurgery for oligomets (<5) is an emerging option.
- The modern RT like IMRT is also helpful for palliative cases.
- Image guided radiotherapy is safer methodology to give high dose RT.







