Evidence and practice changing treatments in genito-urinary tumors

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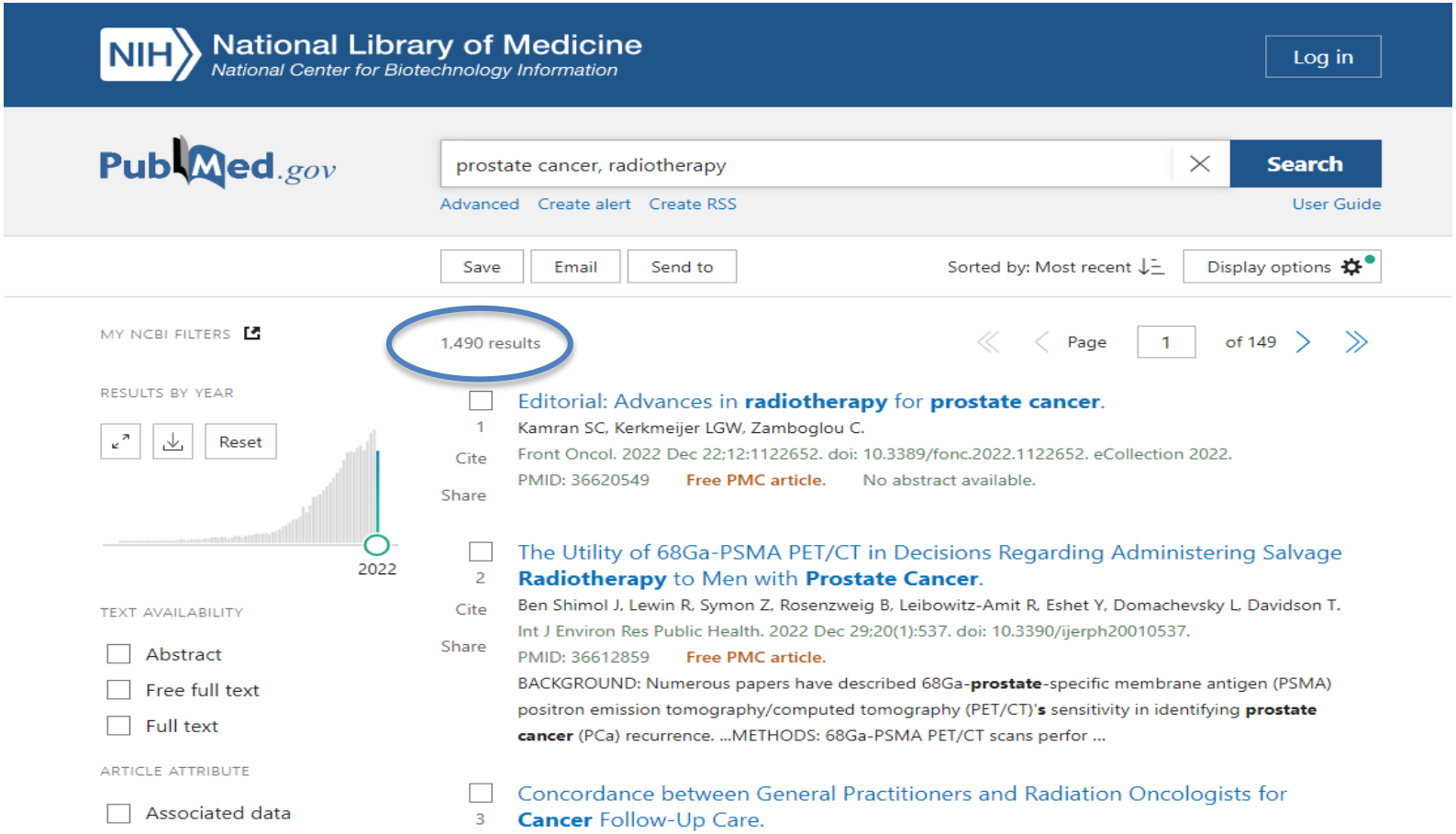
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Editorial: Advances in radiotherapy for prostate cancer.
Kamran SC, Kerkmeijer LGW, Zamboglou C.
Front Oncol. 2022 Dec 22;12:1122652. doi: 10.3389/fonc.2022.1122652. eCollection 2022.
PMID: 36620549 Free PMC article. No abstract available.
2 Cite Share
The Utility of 68Ga-PSMA PET/CT in Decisions Regarding Administering Salvage Radiotherapy to Men with Prostate Cancer.
Ben Shimol J, Lewin R, Symon Z, Rosenzweig B, Leibowitz-Amit R, Eshet Y, Domachevsky L, Davidson T.
Int J Environ Res Public Health. 2022 Dec 29;20(1):537. doi: 10.3390/ijerph20010537.
PMID: 36612859 Free PMC article.
BACKGROUND: Numerous papers have described 68Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT)'s sensitivity in identifying prostate cancer (PCa) recurrence. ...METHODS: 68Ga-PSMA PET/CT scans perfor ...
3
Concordance between General Practitioners and Radiation Oncologists for Cancer Follow-Up Care.

Update degli Studi Practice Changing 2022:

- ✓ PCS5 Trial
- ✓ The Meta-Analysis (MARCAP)
- ✓ RADICAL HD
- ✓ SPPORT Trial
- ✓ Long-term results from the STAMPEDE
- ✓ ARANES TRIAL
- ✓ PEACE 1

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} M1 PC patients

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Multicenter Canadian trial, non-inferiority phase III trial.

329 patients were randomly assigned to receive either conventionally fractionated prostate radiation (76 Gy in 38 daily sessions) or moderately hypofractionated radiation (68 Gy in 25 daily sessions)

PCS5 Trail

329 HR PC pts

≥T3a
PSA ≥ 20 ng/ml
GS 8-10

1:1

Intensity-Modulated CFRT:

76 Gy /2 Gy per fraction to the prostate, 46 Gy/ 2 Gy to the pelvic lymph nodes.

Intensity-Modulated HFRT:

68 Gy / 2.72 Gy per fraction to the prostate, 45 Gy/1.8Gy per fraction to the pelvic lymph nodes.

Acute and delayed GU and GI toxicity differences

Freedom from Biochemical Failure
Disease FS
Overall Survival

All patients received neo-adjuvant, concurrent and adjuvant ADT, with a median duration of 24 months

PCS5 Trail

Results:

HFRT vs CFRT (FU 7 year): researchers found no differences in

- ✓ OS: 81.7% vs 82 (p = .76)
- ✓ PC Specific Mortality: 94.9% vs 96.4% (p = .61)
- ✓ Biochemical Recurrence: 87.4% vs 85.1% (p = .69)
- ✓ DM recurrence: 91.5% vs 91.8% (p = .76), or DFS 86.5% vs 83.4% (p = .50)

- ✓ Side effects were also similar between the treatment arms. No G4 tox in either arm, and no significant differences in G3 short-or long-term GU and GI toxicities

PCS5 Trail

Conclusions:

This is the first hypofractionated RT study in high-risk PCa patients treated with contemporary radiation and ADT. Hypofractionated radiotherapy using 68 Gy in 25 fractions is non-inferior to CF using 76 Gy in 38 fractions and can be considered as a new standard of care for EBRT of high-risk PC.

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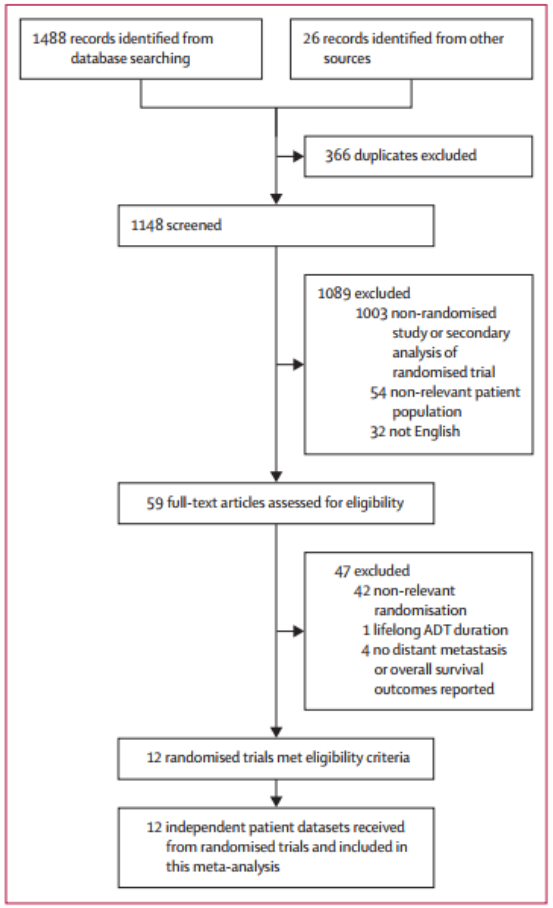
Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis

Amar U Kishan*, Yilun Sun*, Holly Hartman, Thomas M Pisansky, Michel Bolla, Anouk Neven, Allison Steigler, James W Denham, Felix Y Feng, Almudena Zapatero, John G Armstrong, Abdenour Nabid, Nathalie Carrier, Luis Souhami, Mary T Dunne, Jason A Efstathiou, Howard M Sandler, Araceli Guerrero, David Joseph, Philippe Maingon, Theo M de Reijke, Xavier Maldonado, Ting Martin Ma, Tahmineh Romero, Xiaoyan Wang, Matthew B Rettig, Robert E Reiter, Nicholas G Zaorsky, Michael L Steinberg, Nicholas G Nickols, Angela Y Jia, Jorge A Garcia, Daniel E Spratt, the MARCAP Consortium group†

Kishan AU, et al ; MARCAP Consortium group. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol. 2022 Feb;23(2):304-316. Lancet Oncol. 2022 Jul;23(7):e319. PMID: 35051385.



The Meta-Analysis of RCT in Cancer of the Prostate (MARCAP) Consortium was accessed to obtain individual pt data from RCT.

The primary outcome was MFS

1. ADT use (RT alone *vs* RT plus ADT)
2. Neoadjuvant ADT extension (total ADT duration in the neoadjuvant setting from 3–4 months to 6–9 months)
3. Adjuvant ADT prolongation (total ADT duration in the adjuvant setting from 4–6 months to 18–36 months)

Kishan AU, et al ; MARCAP Consortium group. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol. 2022 Feb;23(2):304-316. Lancet Oncol. 2022 Jul;23(7):e319. PMID: 35051385.

It provides 4 novel, clinically relevant insights that were unclear from individual trial results:

1. A significant MFS and OS benefit from the addition of ADT to RT. NNT to prevent 1 DM event at 10 yrs of 8–18 pts treated (high and intermediate)

IR divided into favourable or unfavourable subgroups. This stratification scheme requires information about the % of biopsy cores that were positive, which was not uniformly available across the trials

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Nabid 2021 et al trial was not designed as a noninferiority study.

2. Adjuvant ADT prolongation to at least 18 months in conjunction with RT further improves MFS and OS compared with ST ADT (NNT to prevent 1 distant metastasis of 10 for pts with HR disease)

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3. Extension of neoadjuvant ADT was not associated with improved BR, DM, MFS, OS and thus should not be routinely recommended

4. The treatment effects of each intensification strategy were not significantly affected by radiotherapy dose, NCCN risk group, or patient age (≥70 years vs <70 year)

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An American Society of Clinical Oncology Journal

PROSTATE CANCER - LOCALIZED

Utilization of androgen deprivation therapy (ADT) and stereotactic body radiation therapy (SBRT) for localized prostate cancer (PC) in the United States (US).

The use of SBRT increased significantly for all risk groups from 2004 to 2015, from 0.9% to 10.3% (*P* <.001).

	2004	2015
SBRT overall	0,9%	10,3%
SBRT LR	0,9 %	21,6 %
SBRT FIR	1,1 %	13,7 %
SBRT UIR	0,6%	10,8%
SBRT HR	0,8%	2,8%

During the same time period, the use of ADT decreased among all pts, from 60.8% to 39.2% (P <.001)

	2004	2015
SBRT overall	60,8%	39,2%
SBRT LR	22,8 %	5,5 %
SBRT FIR	51,7 %	40 %
SBRT UIR	53,4%	49,5%
SBRT HR	78,9%	80%

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Across all risk groups, the likelihood of receiving <u>ADT was higher in men who received EBRT than in men who received SBRT</u>.

ADT	RT		SBRT		p-value
	No	Yes	No	Yes	
	N (%)	N (%)	N (%)	N (%)	N (%)
Overall	67976 (50.8)	65849 (49.2)	6393 (84.6)	1166 (15.4)	< 0.001
LR	25755 (86.9)	3895 (13.1)	2511 (95.0)	13 (5.0)	< 0.001
FIR	28454 (57.4)	21157 (42.7)	2732 (85.1)	477 (14.9)	< 0.001
UIR	5476 (51.8)	5094 (48.2)	546 (80.8)	130 (19.2)	< 0.001
HR	8291 (18.9)	35703 (81.2)	604 (58.5)	428 (41.5)	< 0.001

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RADICALS-HD

Examining the effect of differing durations of ADT among men receiving post-operative RT following radical prostatectomy for PC

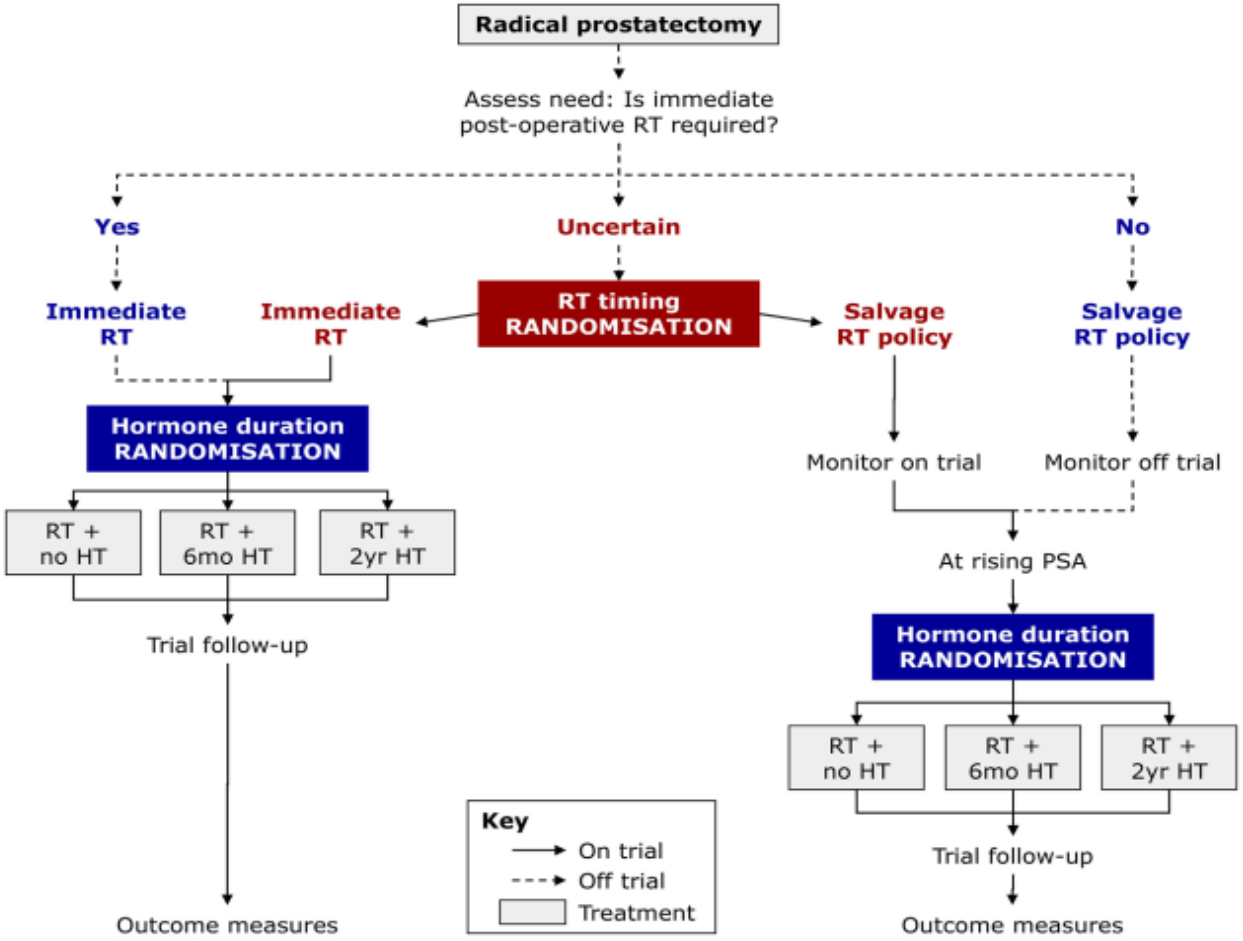
1. Who should have ADT added to their radiotherapy?

2. What is the optimal duration of ADT, short vs long?

RADICALS-HD:
Background

No strong evidence in the adjuvant setting while there is some data from RTOG 9601, GETUF-AFU-16, and RTOG 0534 regarding the use of ADT in the salvage setting for biochemical failure.

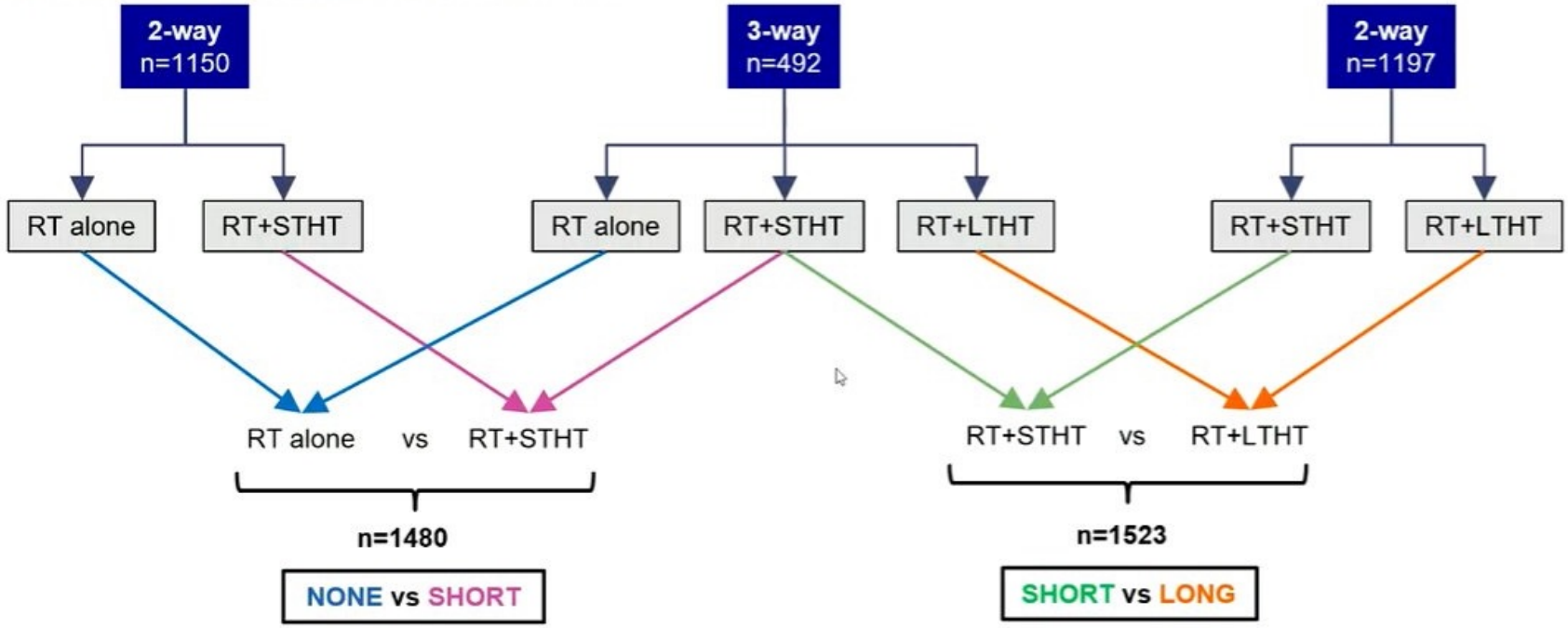
However, this fails to address the question of duration



It is a complex trial design with multiple questions and many comparisons across two different settings (adjuvant and salvage).

RADICALS-HD trial, a randomized comparison assessing questions regarding the use and duration of ADT with postoperative RT, within the RADICALS protocol which also addressed questions relating to the timing of RT (adjuvant *vs* early salvage)

Following RP but prior to the initiation of their RT, pts were randomised to either no ADT (“None”), 6mo ADT (“Short”), or 24mo ADT (“Long”). While, 3-way randomisation was encouraged (to all of the treatment options), 2-way randomisation between both None-vs-Short or Short-vs-Long also allowed.



The trial was powered for the two pairwise comparisons.
The primary outcome measure was metastasis-free survival (MFS) with secondary outcomes including time to salvage ADT and overall survival (OS)

- **RT alone vs RT+STHT**

  NONE vs SHORT

  10-year MFS estimated as **80%** with RT alone
  80% power to detect **6% absolute improvement**: target **HR=0.67**
  200 MFS events required

- **RT+STHT vs RT+LTHT**

  SHORT vs LONG

  10-year MFS estimated as **75%** with RT+STHT
  80% power to **detect 6% absolute improvement**: **target HR=0.72**
  300 MFS events required

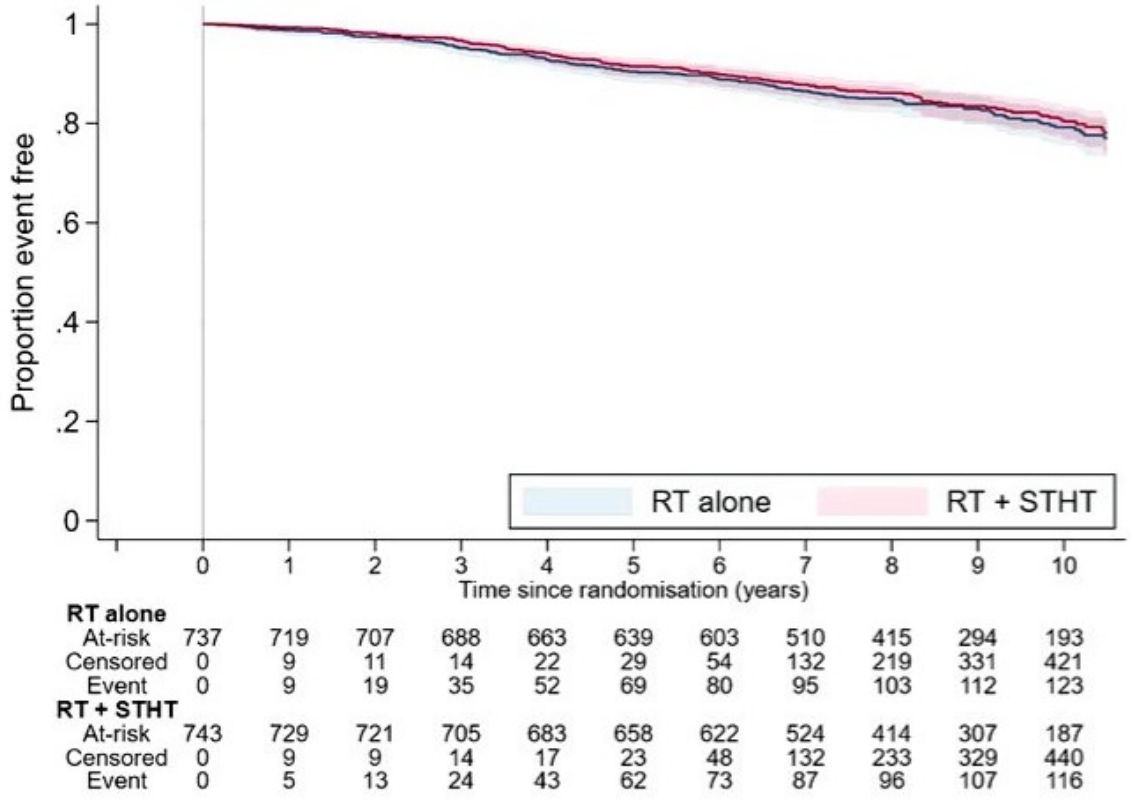
ADT were not standardized and pts and investigators could choose which of the randomizations to participate in.

As expected based on this, pts in the none-vs-short randomization were less likely to have T3b/4 disease or GS 8-10 histology. Rates of 2 or 3 risk factors were much lower as well (16% vs 35%).

RADICALS-HD: Patient Characteristics

		NONE vs SHORT		SHORT vs LONG	
		RT alone (n=737)	RT + STHT (n=743)	RT + STHT (n=761)	RT + LTHT (n=762)
Age	median (IQR)	66 (61-69)	66 (61-69)	65 (60-69)	65 (61-69)
PSA	median (range)	0.22 (0-3.7)	0.2 (0-4.2)	0.22 (0-5)	0.24 (0-4.9)
RT timing	adjuvant	208 (28%)	215 (29%)	328 (43%)	325 (43%)
	early salvage	529 (72%)	528 (71%)	433 (57%)	437 (57%)
T stage	3a	325 (44%)	303 (41%)	327 (43%)	309 (41%)
	3b/4	112 (16%)	128 (17%)	226 (29%)	235 (31%)
Gleason	8-10	83 (11%)	86 (12%)	215 (28%)	219 (29%)
Positive margins	present	452 (61%)	472 (64%)	480 (63%)	484 (64%)
2 or 3 risk factors		15.5%		34.6%	
PSA > 0.5		18.7%		25.7%	

None vs Short: Metastases-Free Survival (MFS)



RT alone										
At-risk	737	719	707	688	663	639	603	510	415	294	193
Censored	0	9	11	14	22	29	54	132	219	331	421
Event	0	9	19	35	52	69	80	95	103	112	123
RT + STHT										
At-risk	743	729	721	705	683	658	622	524	414	307	187
Censored	0	9	9	14	17	23	48	132	233	329	440
Event	0	5	13	24	43	62	73	87	96	107	116

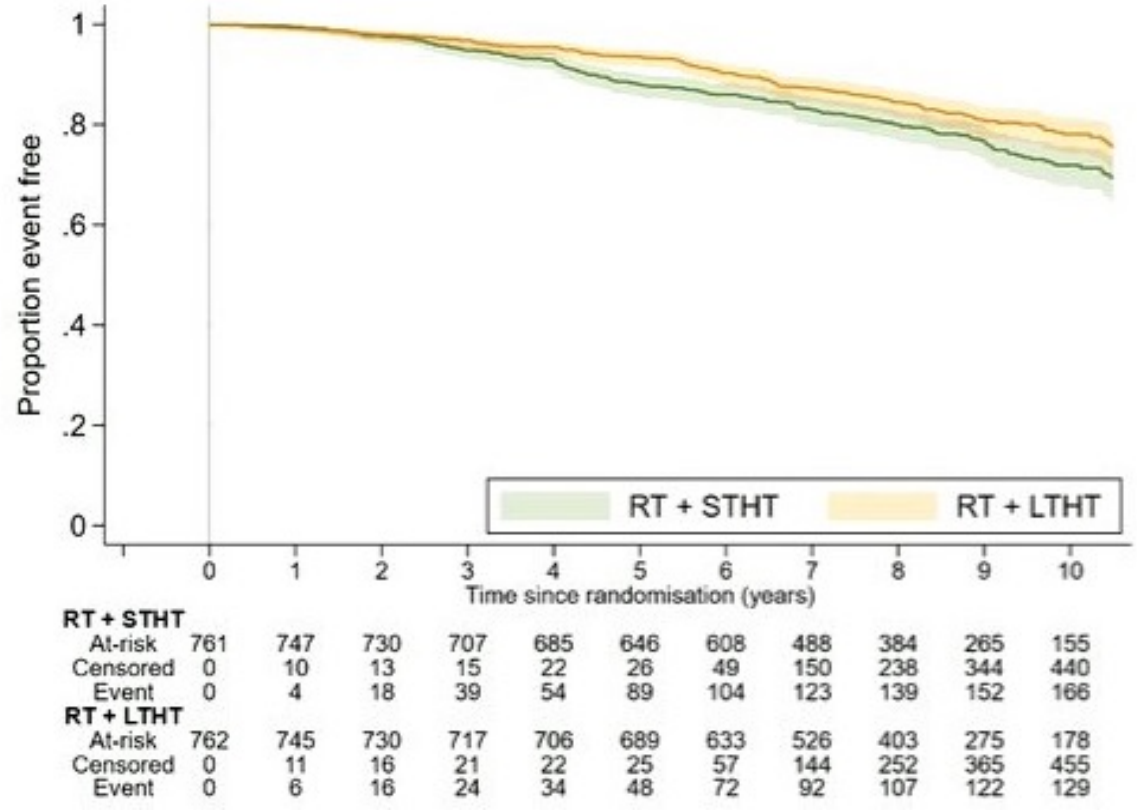
NONE vs SHORT

	RT alone (n=737)	RT+STHT (n=743)
Events	142	126
HR (95%CI)	**0.89** (0.69 to 1.14)	
P-value	0.35	
10yr event free	79%	80%

Note: HR < 1 favour RT+STHT
Note: predicted 10yr MFS = 80%

Median FU of 9 years, in None-vs-Short comparison 6 mos of ADT did not improve MFS compared to no ADT (HR 0.89; CI: 0.69-1.14; 79% vs 80% event-free at 10 years)

Short vs Long: Metastases-Free Survival (MFS)



SHORT vs LONG

	RT+STHT (n=761)	RT+LTHT (n=762)
Events	174	139
HR (95%CI)	**0.77** (0.61 to 0.97)	
P-value	0.03	
10yr event free	72%	78%

Note: HR < 1 favour RT+LTHT
Note: predicted 10yr MFS = 75%

In the comparison of Short-vs-Long duration of ADT, 24 months of ADT improved MFS (HR 0.77; CI: 0.61-0.97; 72% vs 78% at 10yrs), and delayed the time to salvage ADT (HR 0.73; CI: 0.59-0.91).
However, OS was not improved (HR 0.88; CI: 0.66-1.17)

Summarizing these results:

- ✓ Adding short-term ADT to salvage RT in a better-risk population: no incremental improvements in MFS (many patients appear to do well with RT alone)
- ✓ In patients with higher risk disease, the prolongation of ADT treatment from 6 months to 2 years resulted in improvements in MFS. However, many patients in the short-term arm did very well
- ✓ Quality of life data may be important when considering the toxicity of ADT.

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NRG Oncology/RTOG 0534 SPPORT

The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial

Alan Pollack, Theodore G Karrison, Alexander G Balogh, Leonard G Gomella, Daniel A Low, Deborah W Bruner, Jeffrey S Wefel, Andre-Guy Martin, Jeff M Michalski, Steve J Angyalfi, Himanshu Lukka, Sergio L Faria, George B Rodrigues, Marie-Claude Beauchemin, R Jeffrey Lee, Samantha A Seaward, Aaron M Allen, Drew C Monitto, Wendy Seiferheld, Oliver Sartor, Felix Feng, Howard M Sandler

Pollack A, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet. 2022 May 14;399(10338):1886-1901.

NRG Oncology/RTOG 0534 SPPORT

Eligible pts:
persistently detectable or an initially undetectable and rising PSA
of between 0·1 and 2·0 ng/mL, with and
without lymphadenectomy (pN0/Nx but no c/pN1)
The primary endpoint was freedom from progression at
5 yrs defined as the
first occurrence of biochemical failure(
Phoenix definition)
clinical failure (regional/distant metastasis), or death from any cause.

STRATIFY	RANDOMIZE
SV Involvement 1. No 2. Yes **Prostatectomy Gleason Score** 1. Gleason ≤ 7 2. Gleason 8-9 **Pre-Radiotherapy PSA** 1. PSA ≥ 0.1 and ≤ 1.0 ng/mL 2. PSA > 1.0 and < 2.0 ng/mL **Pathology Stage** 1. pT2 and margin negative 2. All others	**Arm 1: PBRT Alone** PBRT 64.8-70.2 Gy **Arm 2: PBRT + STAD** PBRT 64.8-70.2 Gy + STAD for 4-6 months beginning 2 months before RT **Arm 3: PLNRT + PBRT + STAD** PLNRT to 45 Gy and PBRT to 64.8-70.2 Gy,+ STAD for 4-6 months beginning 2 months before RT

SV = seminal vesicle; RT = radiotherapy; PBRT = prostate bed RT; PLNRT = pelvic lymph node RT; STAD = neoadjuvant and concurrent short term androgen deprivation

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Group 1 Group 2 Group 3

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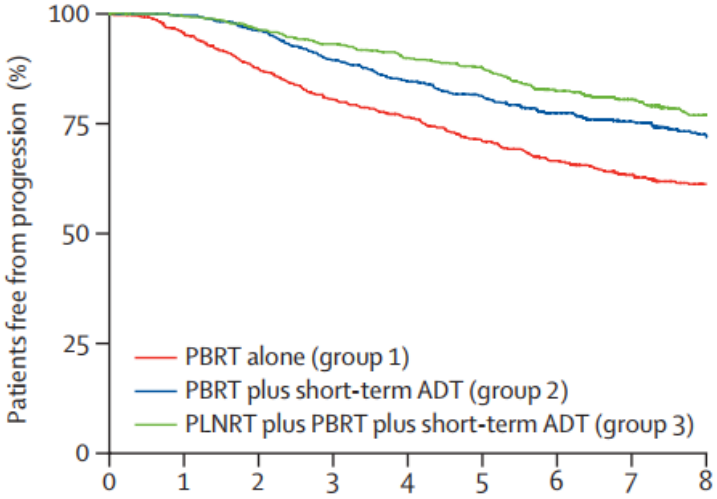
1792 eligible patients were enrolled

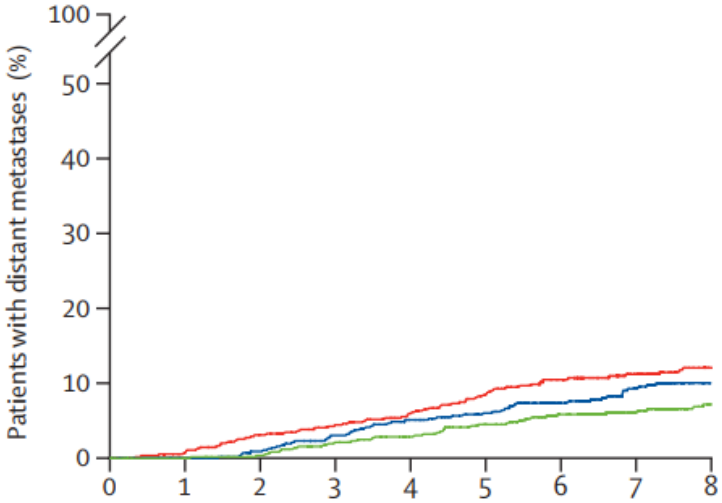
Freedom From Progression



5-year rate
Group 1: 70·9% (95% CI 67·0–74·9)
Group 2: 81·3% (95% CI 78·0–84·6)
Group 3: 87·4% (95% CI 84·7–90·2)

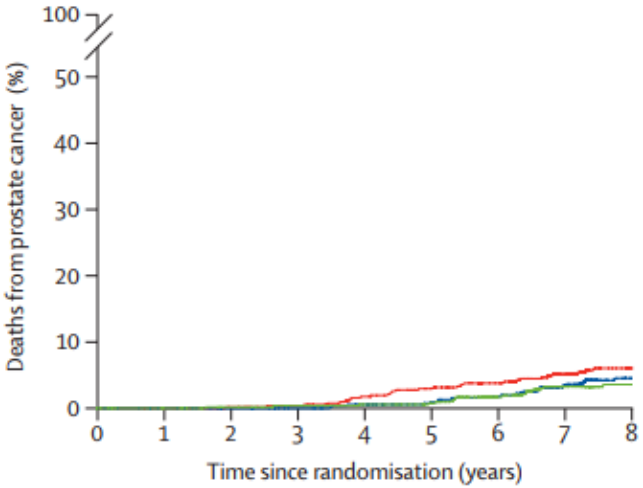
5-year rate comparisons:
Group 3 *vs* group 1: p<0·0001
Group 2 *vs* group 1: p<0·0001
Group 3 *vs* group 2: p=0·0027

Distant Metastasis



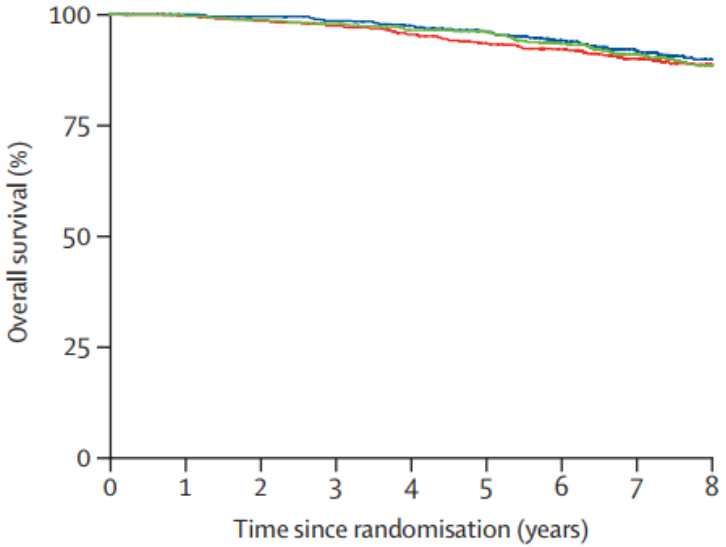
Log-rank tests:
Group 3 *vs* group 1: p=0·0098
Group 2 *vs* group 1: p=0·083
Group 3 *vs* group 2: p=0·043

Prostate Cancer Death



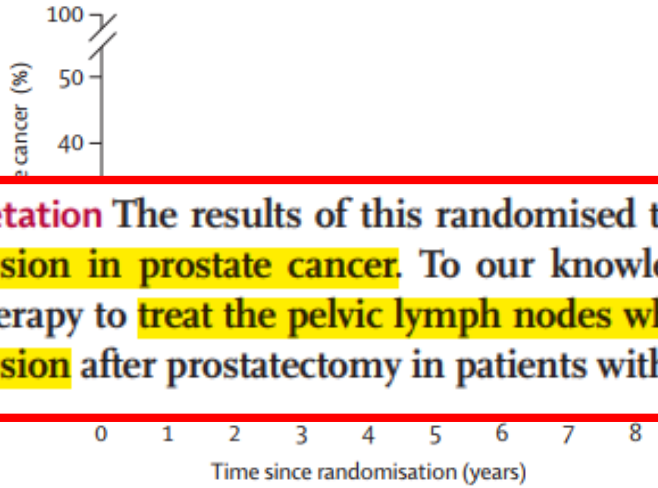
Log-rank tests:
Group 3 *vs* group 1: p=0·012
Group 2 *vs* group 1: p=0·168
Group 3 *vs* group 2: p=0·100

Overall Survival



Log-rank tests:
Group 3 *vs* group 1: p=0·353
Group 2 *vs* group 1: p=0·245
Group 3 *vs* group 2: p=0·620

Prostate Cancer Death



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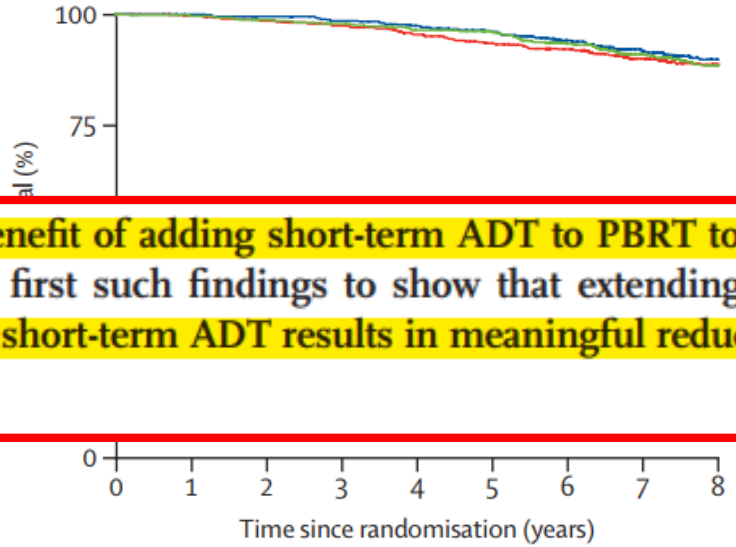

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Interpretation The results of this randomised trial establish the benefit of adding short-term ADT to PBRT to prevent progression in prostate cancer. To our knowledge, these are the first such findings to show that extending salvage radiotherapy to treat the pelvic lymph nodes when combined with short-term ADT results in meaningful reductions in progression after prostatectomy in patients with prostate cancer.

Pelvic lymphadenectomy			
No	189 (34%)	207 (36%)	209 (36%)
Yes	375 (67%)	371 (64%)	365 (64%)

Pelvic lymphadenectomy is primarily a diagnostic and staging method

Pathological tumour stage			
T2	292 (52%)	317 (55%)	304 (53%)
pT3 extraprostatic extension NOS	13 (2%)	15 (3%)	18 (3%)
pT3a extraprostatic extension	177 (31%)	162 (28%)	166 (29%)
pT3b seminal vesicle invasion	82 (15%)	84 (15%)	86 (15%)

Pre-radiotherapy baseline PSA (ng/mL)			
Mean	0·47 (0·38)	0·51 (0·39)	0·47 (0·37)
Median	0·32 (0·20–0·60)	0·40 (0·23–0·68)	0·32 (0·20–0·60)
Range	0·1–1·96	0·1–1·93	0·1–1·93
≥0·1 to ≤0·2 ng/mL	155 (28%)	126 (22%)	154 (27%)
>0·2 to ≤0·5 ng/mL	247 (44%)	256 (44%)	247 (43%)
>0·5 to ≤1·0 ng/mL	105 (19%)	130 (23%)	114 (20%)
>1·0 to <2·0 ng/mL	57 (10%)	66 (11%)	59 (10%)

NRG Oncology/RTOG 0534 SPPORT

Eligible pts:
persistently detectable or an initially undetectable and rising PSA of between 0·1 and 2·0 ng/mL. Pts with and without lymphadenectomy (pN0/Nx but no c/pN1)
The primary endpoint was freedom from progression at 5 yrs defined as the first occurrence of biochemical failure according to the Phoenix definition, clinical failure (regional or distant metastasis), or death from any cause.

STRATIFY	RANDOMIZE
SV Involvement 1. No 2. Yes **Prostatectomy Gleason Score** 1. Gleason ≤ 7 2. Gleason 8-9 **Pre-Radiotherapy PSA** 1. PSA ≥ 0.1 and ≤ 1.0 ng/mL 2. PSA > 1.0 and < 2.0 ng/ml **Pathology Stage** 1. pT2 and margin negative 2. All others	**Arm 1: PBRT Alone** PBRT 64.8-70.2 Gy **Arm 2: PBRT + STAD** PBRT 64.8-70.2 Gy + STAD for 4-6 months beginning 2 months before RT **Arm 3: PLNRT + PBRT + STAD** PLNRT to 45 Gy and PBRT to 64.8-70.2 Gy,+ STAD for 4-6 months beginning 2 months before RT

SV = seminal vesicle; RT = radiotherapy; PBRT = prostate bed RT; PLNRT = pelvic lymph node RT; STAD = neoadjuvant and concurrent short term androgen deprivation

Pollack A, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet. 2022 May 14;399(10338):1886-1901.

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ORIGINAL RESEARCH Open Access

Pre-test ^{68}Ga-PSMA-ligand PET/CT positivity in early biochemical recurrent prostate cancer after radical prostatectomy—validation of a prediction model

Pia Kraft[1], Tobias Maurer[2,4], Andrei Gafita[1], Markus Krönke[1], Bernhard Haller[3], Wolfgang A. Weber[1], Matthias Eiber[1] and Isabel Rauscher[1*]

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Table 2 Subgroup analysis of pre-test probability and actual positive findings in ^{68}Ga-PSMA-11-ligand PET

Patient subgroup	Compact model pre-test probability	Comprehensive model pre-test probability	Positive imaging findings
Entire cohort	67% (95% CI 65–68%)	69% (95% CI 66–71%)	69% (201/292)
Very low PSA (0.2–0.5 ng/ml)	57% (95% CI 55–60%)	59% (95% CI 56–61%)	59% (89/151)
Low PSA (> 0.5–1 ng/ml)	72% (95% CI 70–74%)	74% (95% CI 72–76%)	79% (112/141)

Table 3 Localization of positive findings on ^{68}Ga-PSMA-11-ligand PET according to PSA range

PSA range	0.2–0.5 ng/ml (very low)		> 0.5–1.0 ng/ml (low)		*p* value
	No.	%	No.	%	
Total no. of patients with positive findings	89/151	58.9	112/141	79.4	0.0003*
Localization of positive findings on ^{68}Ga-PSMA-11-ligand PET					
Local	24/151	15.9	38/141	27.0	0.0297*
LN pelvic/retroperitoneal	58/151	38.4	73/141	51.8	0.0290*
LN supradiaphragmal	7/151	4.6	7/141	5.0	0.9091
Bone	30/151	19.9	28/141	19.9	0.8834
Visceral	2/151	1.3	4/141	2.8	0.6215

*Significant difference $p \leq 0.05$

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- ✓ PCS5 Trial
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- ✓ SPPORT Trial
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- ✓ ARANES TRIAL
- ✓ PEACE 1

M1 PC patients

RT mHSPC LOW VOLUME

PLOS MEDICINE

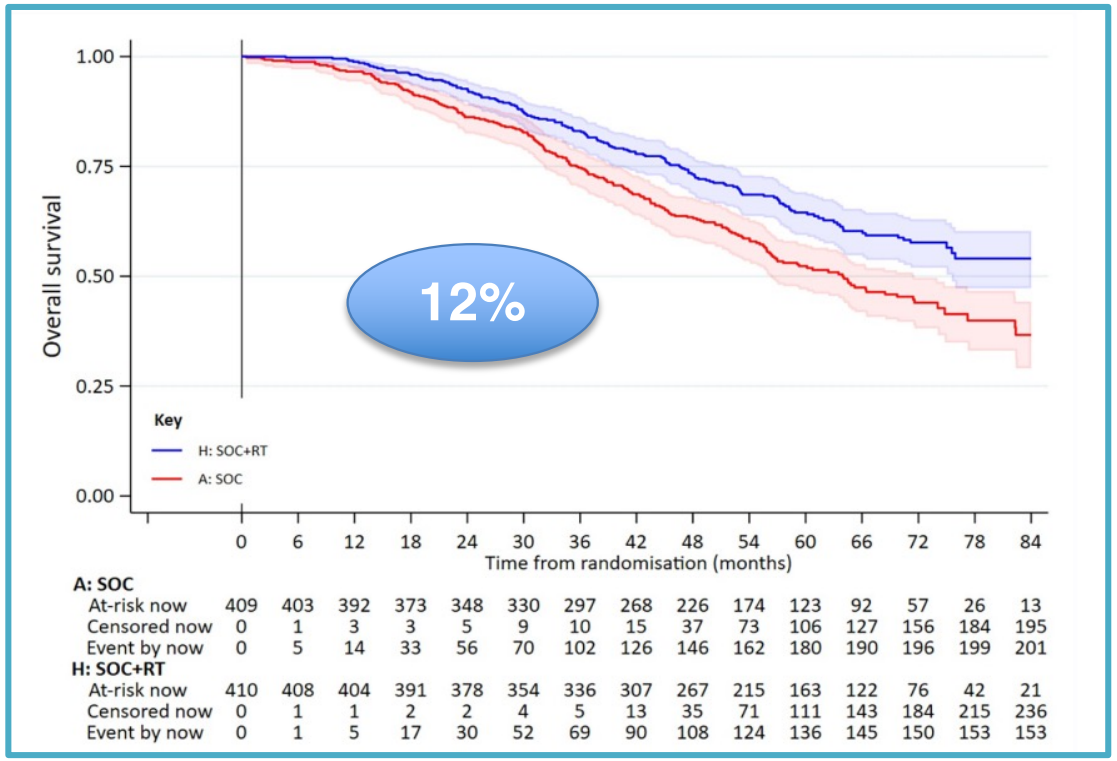
RESEARCH ARTICLE

Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial

In the low metastatic burden group: median OS was 63.6 months for SOC and 85.5 months for SOC+RT (5-year survival 53% versus 65%); adjusted HR = 0.64 (95% CI 0.52 to 0.79; p <0.001 [p = 0.00004])

Parker CC, et al R; STAMPEDE Trial Collaborative Group. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial. PLoS Med. 2022 Jun 7

median FU of 61.3 months



RT mHSPC LOW VOLUME

Table 4. Patients with grade 3/4 worst late RT toxicity score reported over entire time on trial.

Toxicity area	SOC+RT	
	Weekly, 36 Gy/6 f (*n* = 473)	Daily, 55 Gy/20 f (*n* = 517)
Urinary	**10 (2%)**	**10 (2%)**
Hematuria	4 (1%)	4 (1%)
Urethral stricture	3 (1%)	4 (1%)
Cystitis	3 (1%)	4 (1%)
Bowel	**15 (3%)**	**11 (2%)**
Proctitis	9 (2%)	5 (1%)
Diarrhea	6 (1%)	6 (1%)
Rectal–anal stricture	0 (0%)	0 (0%)
Rectal ulcer	0 (0%)	1 (<1%)
Bowel obstruction	1 (<1%)	1 (<1%)

Note: SOC+RT in safety population (RTOG scale; patients with RT started within 1 year of randomisation). There were no reported grade 5 late RT toxicity events.
RT, radiotherapy to the prostate; SOC, standard of care.

Parker CC, et al R; STAMPEDE Trial Collaborative Group. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial. PLoS Med. 2022 Jun 7

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M1 PC patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

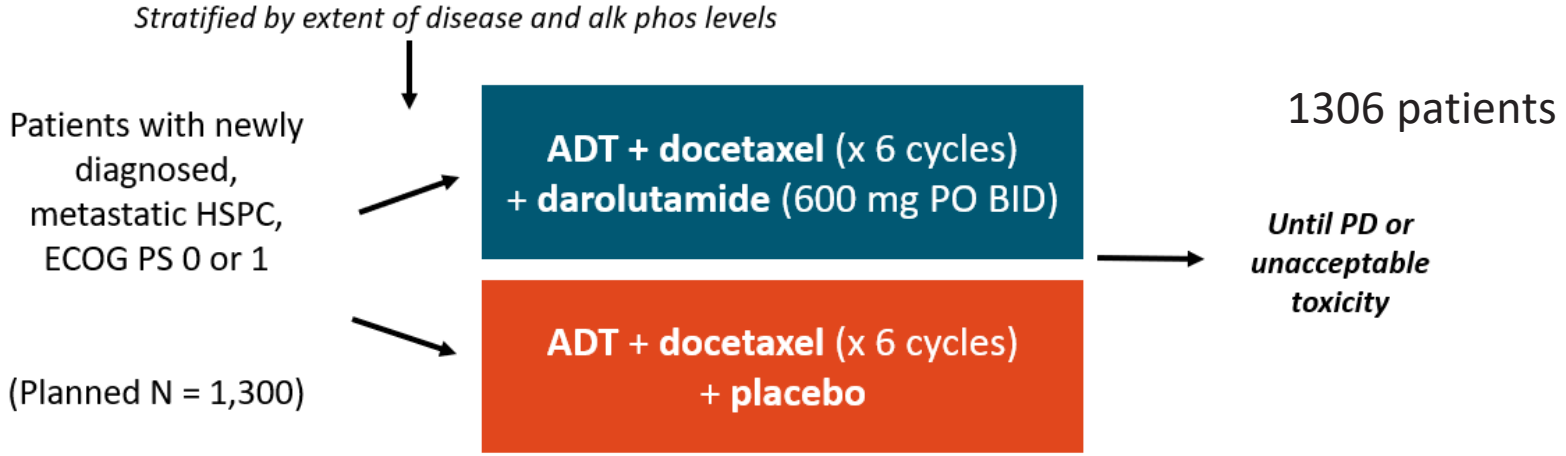
Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

Smith MR, et al. ARASENS Trial Investigators. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022 Mar 24;386(12):1132-1142. Epub 2022 Feb 17

ARASENS Phase 3 Trial: Darolutamide in mHSPC

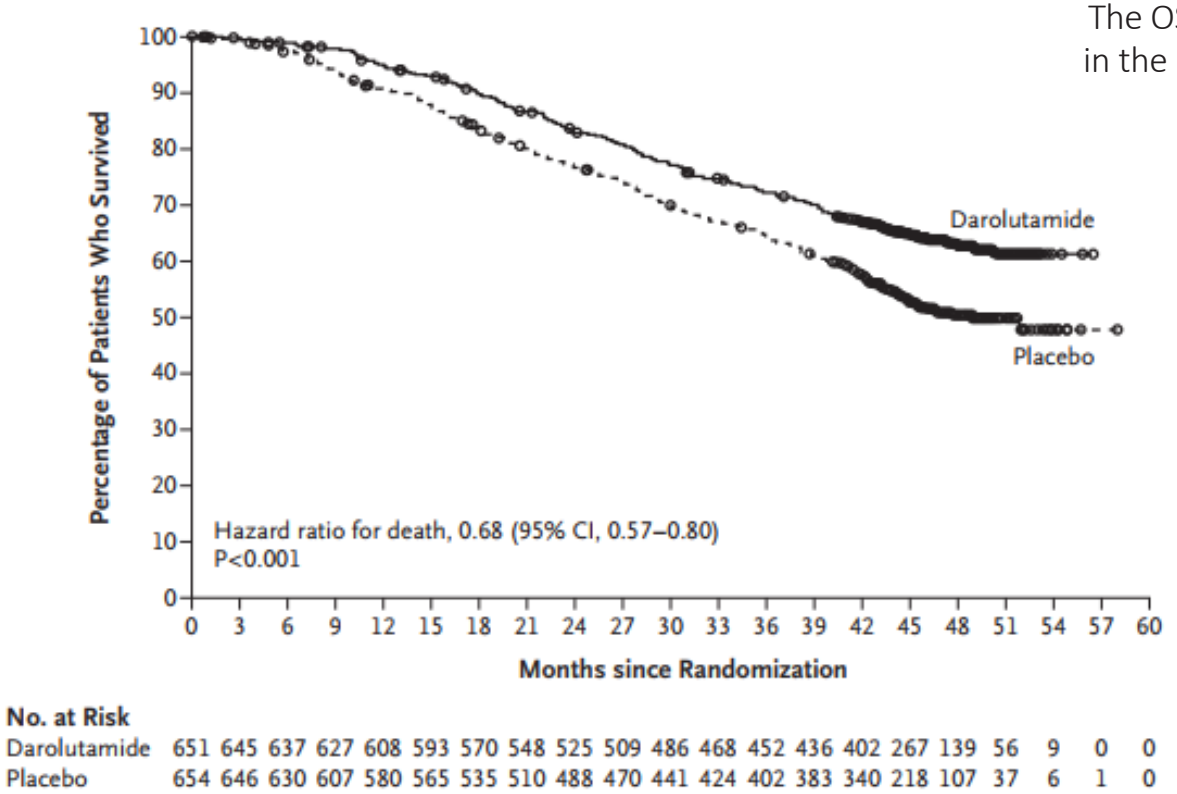
- Randomized, double-blind, placebo controlled, international trial > 300 sites in 23 countries



- Primary endpoint: OS
- Secondary endpoints: Time to CRPC, time to initiation of subsequent anticancer therapy, SSE-free survival, time to first SSE, time to first opioid use, time to pain progression, and time to worsening of physical symptoms

Smith MR, et al. ARASENS Trial Investigators. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022 Mar

The OS at 4 years was 62.7% (95% CI, 58.7 to 66.7) in the Darolutamide group and 50.4% (95% CI, 46.3 to 54.6) in the placebo group



	Median Survival (95% CI)
	mo
Darolutamide	NE
Placebo	48.9 (44.4–NE)

Smith MR, et al. ARASENS Trial Investigators. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022 Mar 24;386(12):1132-1142. Epub 2022 Feb 17.

mHSPC: Trial clinici

Trial[1]	Comparator Arm	Control Arm	N	HR for PFS (or Other Endpoint)	HR for OS
Docetaxel					
▪ CHAARTED[2]	ADT + Doc	ADT	513	0.58 (time to CRPC)	0.63
▪ GETUG-15[3]	ADT + Doc	ADT	183	NA	0.78
▪ STAMPEDE Arm C[4]	ADT + Doc	ADT	148	NA	0.81
AR Pathway Inhibitors					
▪ LATITUDE[5]	ADT + ABI + Pred	ADT	955	NA	0.62
▪ STAMPEDE Arm G[6]	ADT + ABI + Pred	ADT	473	0.31 (FFS)	0.54
▪ ENZAMET[7]	ADT + ENZA (± Doc)	ADT + NSAA (± Doc)	588	0.45	0.80
▪ ARCHES[8]	ADT + ENZA*	ADT*	727	0.43 (rPFS)	TBD
▪ TITAN[9]	ADT + APA*	ADT*	660	0.53	0.68
RT					
▪ STAMPEDE Arm H[10]	ADT + RT to prostate	ADT (+ DOC possible)	1120	NA	1.07
▪ HORRAD[11]	ADT + RT to prostate	ADT	272	NA	1.06

1.VanderWeele. JCO. 2019;37:2961. 2. Kyriakopoulos. JCO. 2018;36:1080. 3. Gravis. Eur Urol. 2016;70:256. 4. Clark. Ann Oncol. 2019;30:1992. 5. Fizazi. Lancet Oncol. 2019;20:686. 6. Hoyle. Eur Urol. 2019;76:719. 7. Davis. NEJM. 2019;381:121. 8. Armstrong. JCO. 2019;37:2974. 9. Chi. NEJM. 2019;381:13. 10. Parker. Lancet. 2018;392:2353. 11. Boevé. Eur Ur2019;75:410

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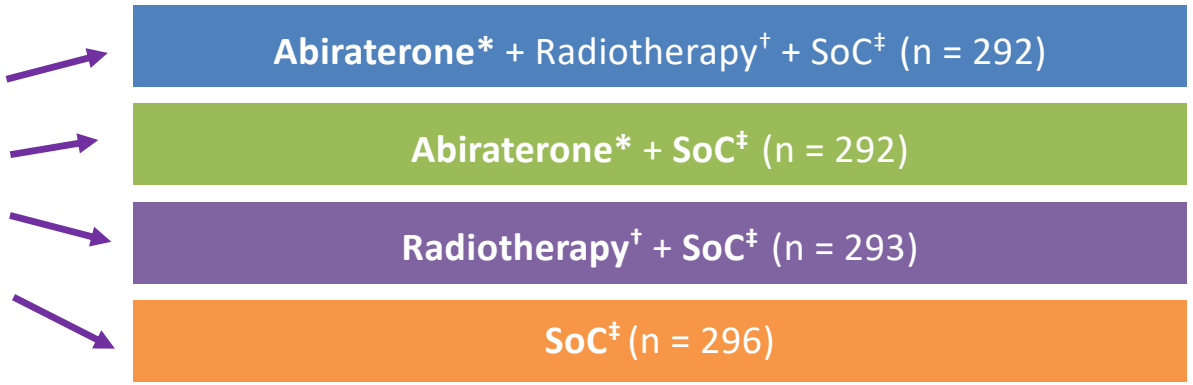
M1 PC patients

PEACE-1

Multicenter, European, randomized, open-label phase III trial

Stratified by ECOG PS (0 vs 1/2), metastatic site (LN vs bone vs visceral), type of castration (surgical vs LHRH agonist), docetaxel (yes vs no)

Patients with de novo mCSPC; distant mets by ≥1 lesion on bone scan and/or CT scan; ECOG PS 0-2; continuous on-study ADT; ADT for ≤3 mo before enrolment permitted (N = 1173)



*Abiraterone 1000 mg/day + prednisone 5 mg BID until PD or intolerance. †74 Gy in 37 fractions. ‡Continuous ADT ± docetaxel 75 mg/m^2 Q3W x 6 cycles. In 2015, trial was amended to allow docetaxel use. In 2017, trial was amended to make docetaxel mandatory for SoC.

- Co-primary endpoints: rPFS and OS with 2x2 factorial design and hierarchical testing
- Key secondary endpoints: castration resistance-free survival, time to next SRE, PSA response rate, time to pain progression, QoL, safety

PEACE-1

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Stratified by ECOG PS (0 vs 1/2), metastatic site (LN vs bone vs visceral), type of castration (surgical vs LHRH agonist vs LHRH antagonist), docetaxel (yes vs no)

Abiraterone* + Radiotherapy† + SoC‡ (n = 292)

Radiotherapy to the prostate was delivered in 37 doses to a cumulative dose of 74 Gy after patients completed docetaxel if receiving chemotherapy.

*Abiraterone 1000 mg/day + prednisone 5 mg BID until PD or intolerance. †74 Gy in 37 fractions. ‡Continuous ADT ± docetaxel 75 mg/m^2 Q3W x 6 cycles. In 2015, trial was amended to allow docetaxel use. In 2017, trial was amended to make docetaxel mandatory for SoC.

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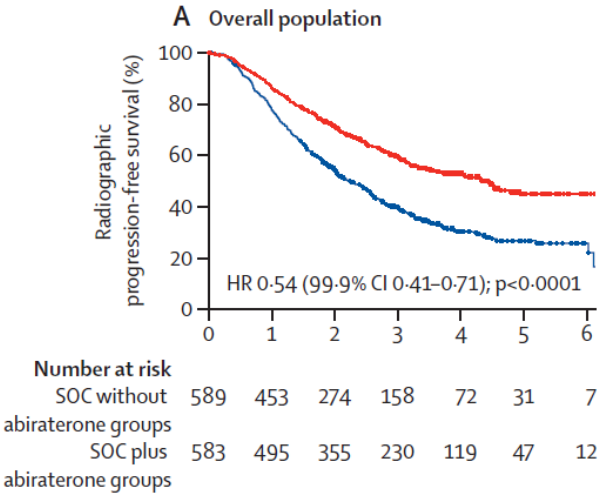
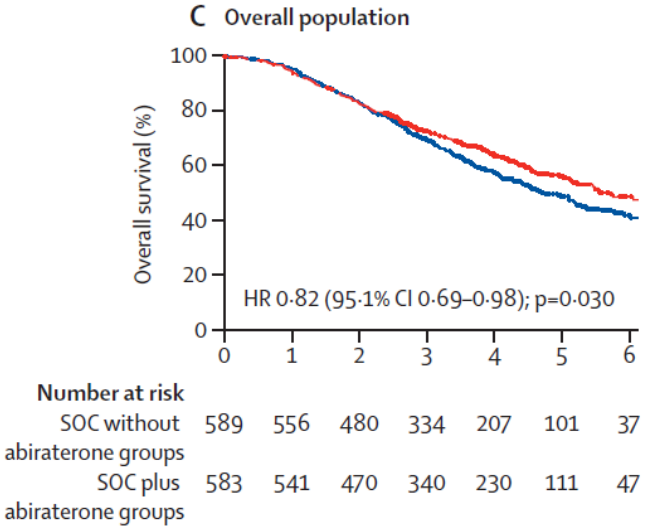
Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

*Karim Fizazi, Stéphanie Foulon, Joan Carles, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Loic Mourey, Brigitte Laguerre, Sophie Abadie-Lacourtoisie, Etienne Martin, Claude El Kouri, Anne Escande, Alvar Rosello, Nicolas Magne, Friederike Schlurmann, Frank Priou, Marie-Eve Chand-Fouche, Salvador Villà Freixa, Muhammad Jamaluddin, Isabelle Rieger, Alberto Bossi, on behalf of the PEACE-1 investigators**





In the overall cohort, the ADT +/- docetaxel +/- RT + abiraterone arm (SOC + abi) was associated with a statistically significant improvement in rPFS relative to ADT +/- docetaxel +/- RT (SOC). Specifically, rPFS improved from a median of 2.2 years to 4.5 years, conferring a hazard ratio for progression of 0.54 (95% CI 0.46-0.64, p < 0.0001)

Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

*Karim Fizazi, Stéphanie Foulon, Joan Carles, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Loic Mourey, Brigitte Laguerre, Sophie Abadie-Lacourtoisie, Etienne Martin, Claude El Kouri, Anne Escande, Alvar Rosello, Nicolas Magne, Friederike Schlurmann, Frank Priou, Marie-Eve Chand-Fouche, Salvador Villà Freixa, Muhammad Jamaluddin, Isabelle Rieger, Alberto Bossi, on behalf of the PEACE-1 investigators**

mCSPC. Our findings cannot directly address whether this triplet systemic combination is superior to ADT and abiraterone. Longer follow-up is required to answer whether combining such an intensive first line systemic treatment with radiotherapy to the primary tumour might provide further clinical benefits for patients with mCSPC. This upcoming analysis will be performed when the preplanned number of radiographic progression-free survival and overall survival events is reached in the population of men presenting with low-volume metastatic dissemination.

Take Home Message

Localised PC

Hypofractionated RT can be considered as a new SOC for EBRT of high-risk PC.
(SBRT and Hypo moderate in low and intermediate risk PC)

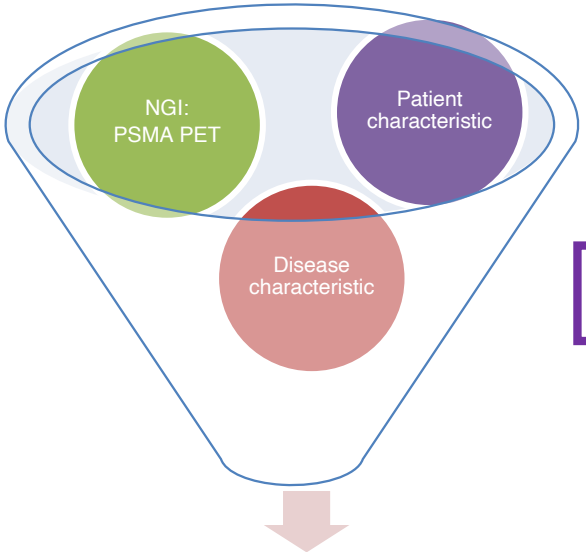
No more 2 Gy!

Benefit from the addition of ADT to RT:
- 6m in UHR PC
- 18/24-36 months in HR PC

Intensification strategy were not significantly affected by RT dose, patient age (≥70 years vs <70 year)

Take Home Message

Postoperative management



Personalized medicine

- RT time: adjuvant vs Early savage
Volume (ENRT or no)
-ADT (None vs Short vs Long)

Take Home Message

Postoperative management

- ✓ eSRT and adjuvant radiotherapy offer similar outcomes for event-free survival.
- ✓ Salvage radiotherapy spares many men from receiving radiotherapy and associated side-effects.
- ✓ Adjuvant RT: highest risk factors
- ✓ ADT: salvage RT (HR factors)
- ✓ ENRT: PSMA PET?

Take Home Message

M1 PC patients

ADT + X
- Docetaxel
- ARTA (Apalutamde Enzalutamide)
- Docetaxel + ARTA

ADT + X + Y
- RT sulla prostata (mHSPC low volume)
- SBRT (metacrono > de novo low volume)

ADT alone is no longer the SOC!

Grazie per la vostra attenzione