

Le novità nel trattamento radioterapico del tumore della prostata

**Dott.ssa Suela Vukcaj
UOC Radioterapia
ASST PAPA GIOVANNI XXIII
svukcaj@asst-pg23.it**

I NUMERI
DEL CANCRO
IN ITALIA
2023



PROSTATA

Incidenza

Nel 2023, sono state stimate circa 41.100 nuove diagnosi. Le neoplasie prostatiche sono le più frequenti nell'uomo (19,8% di tutti i tumori maschili)

Mortalità

Nel 2022, sono stimati 8.200 decessi per tumore della prostata. Le stime per il 2023 non sono disponibili

Sopravvivenza netta a 5 anni dalla diagnosi

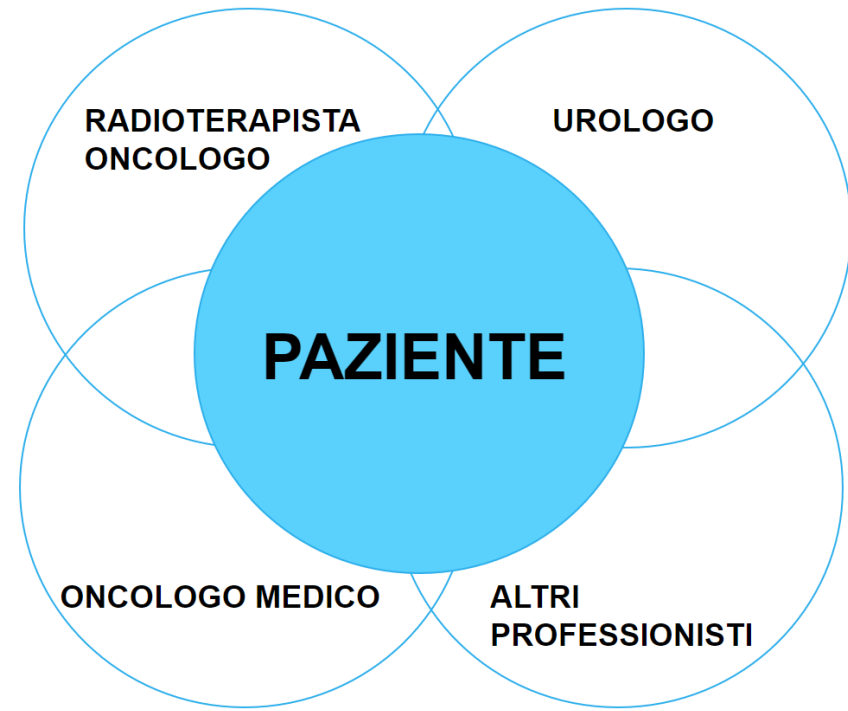
91%

Probabilità di vivere ulteriori 4 anni condizionata ad aver superato il primo anno dopo la diagnosi

94%

Prevalenza

Sono 564.000 gli uomini viventi in Italia dopo una diagnosi di tumore della prostata

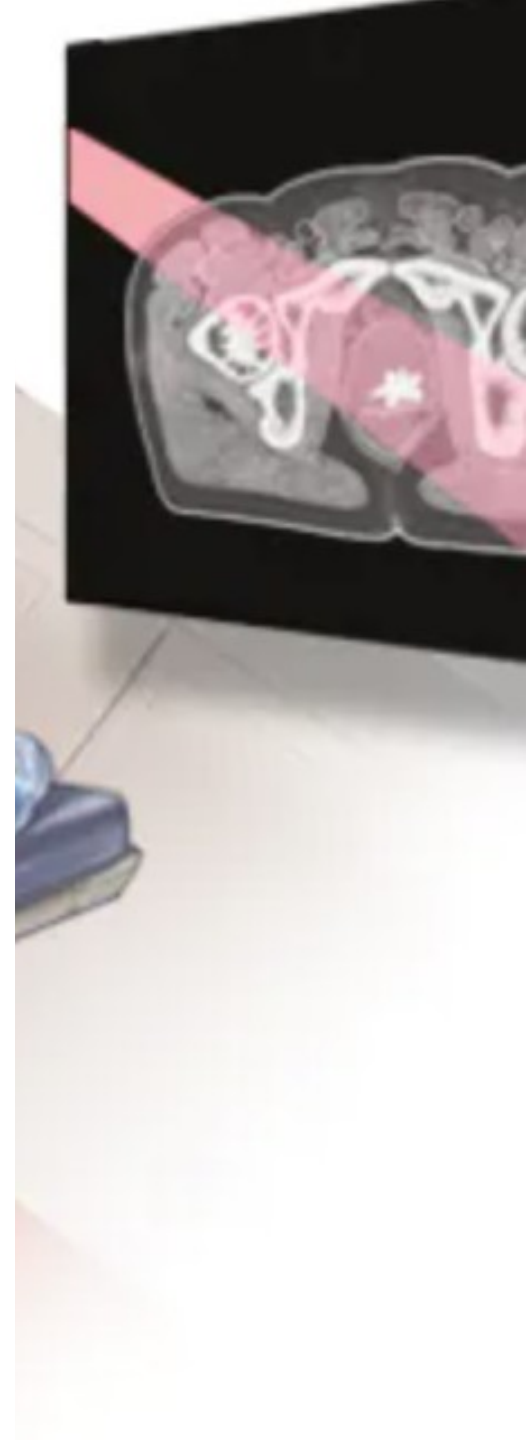


Le opzione terapeutiche

- Chirurgia
- Radioterapia
- Terapia sistemica



La Radioterapia...



Finalità del trattamento radioterapico

Finalità curativa esclusiva

Finalità curativa adiuvante

Finalità curativa di salvataggio

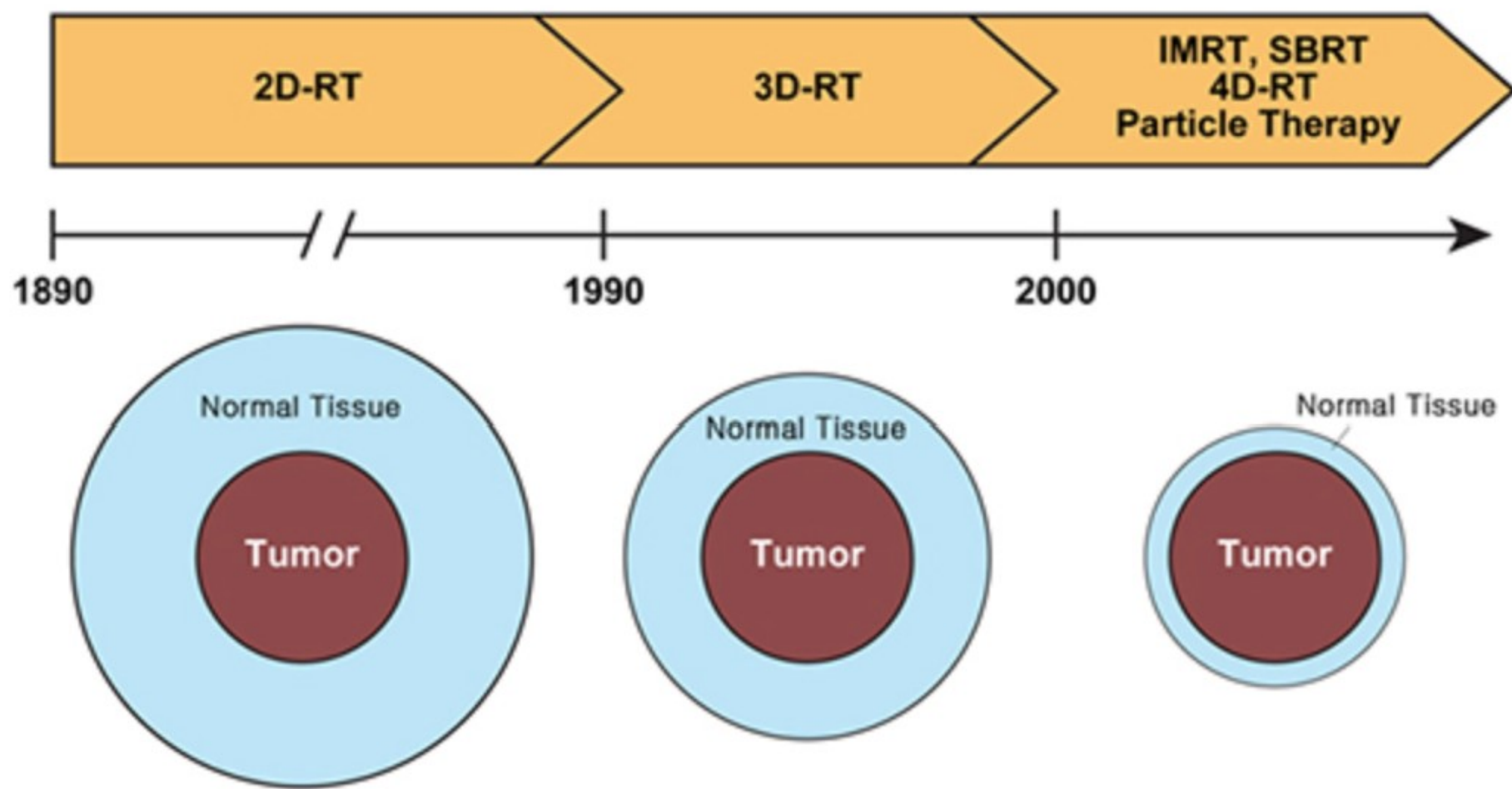
Finalità palliativa



Può essere utilizzata come unico trattamento oppure in combinazione con altre terapie mediche.

Radioterapia curativa esclusiva

EVOLUTION OF MODERN RADIOTHERAPY



Modern radiotherapy is characterized by minimizing the volume of normal tissue being unnecessarily irradiated

Total treatment duration

Conventional radiotherapy



Moderate hypofractionation



Extreme hypofractionation



	Fractionation schedule		
	Conventional	Moderate	Extreme
Total dose (Gy)	76–80	57–70.2	38–50
Total treatment duration (weeks)	8–9	4–6	1–2
Number of fractions (n)	38–40	19–30	4–5
Dose per fraction (Gy)	1.8–2	2.4–4	6–10
Interval between fractions (days)	1	1	1–2

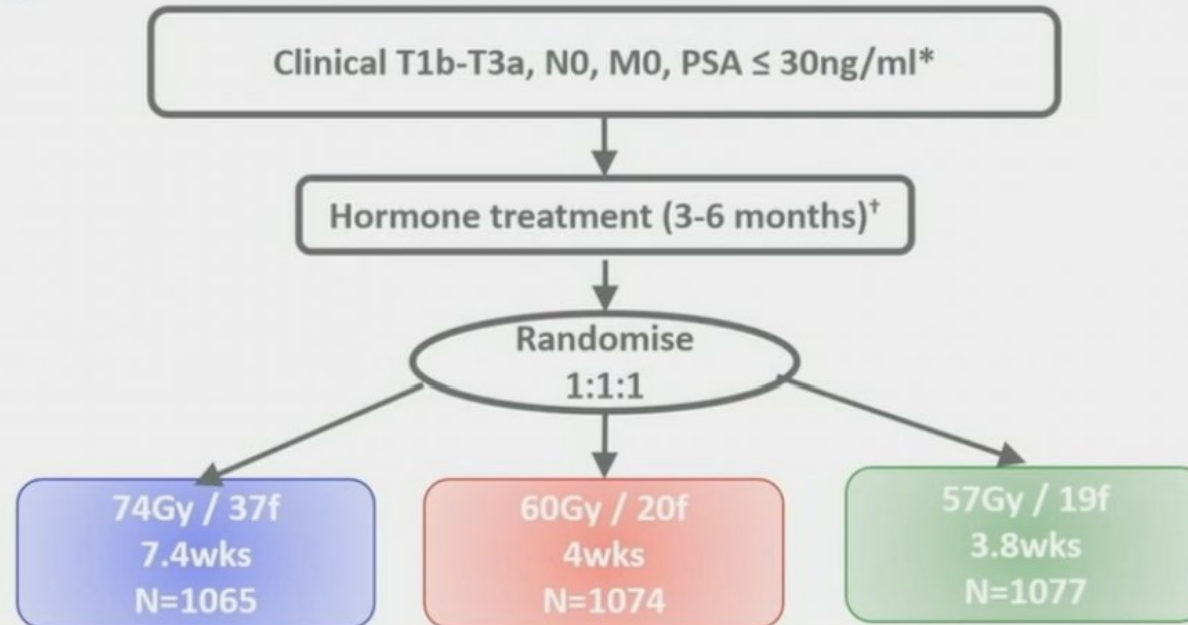
Nature Reviews | Urology

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

Lancet Oncol 2016; 17: 1047-60

Trial Schema

3



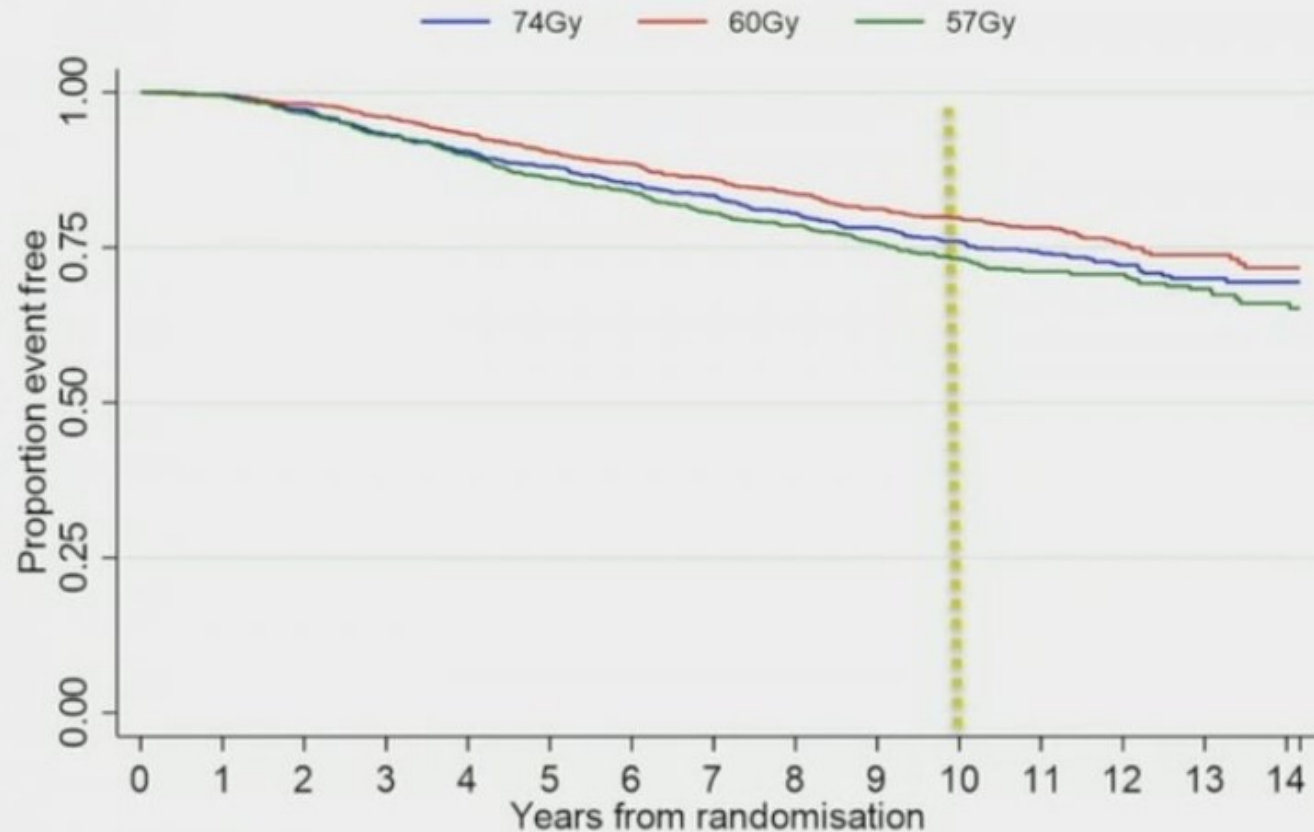
† optional for patients with low risk disease

*Risk of seminal vesicle involvement ≤ 30% (PSA+[GS-6] x10)

Non-inferiority design with a critical hazard ratio of 1.21 for each hypofractionated schedule compared to 74Gy/37f

ASCO GU 2023: 10-Year Efficacy and Co-Morbidity Outcomes of a Phase III Randomised Trial of Conventional vs. Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP; CRUK/06/016)

Biochemical failure/PC recurrence: Non-inferiority analysis



Lancet Oncology 2016*

- 5.2 years median follow-up
- 417 primary endpoint events

Snapshot taken Jan 2023

- 12.1 years median follow-up
- 772 primary endpoint events

10 year event-free rates:

- 74Gy: 76.0% (95%CI 73.1-78.6)
- 60Gy: 79.8% (95%CI 77.1-82.3)
- 57Gy: 73.1% (95%CI 70.2-75.9)

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial



Lancet 2019; 394: 385-95



Material and methods – trial design

- Open, randomised, phase III trial
 - Intermediate/high-risk prostate cancer*
 - 1200 patients accrued
 - July 2005-Nov 2015
 - No androgen deprivation therapy

R
A
N
D
O
M
I
S
E

Conventional fractionation
(CF): $39 \times 2.00 \text{ Gy} = 78.0 \text{ Gy}$
over 8 weeks

Ultrahypofractionation
(U-HF): $7 \times 6.10 \text{ Gy} = 42.7 \text{ Gy}$
over 2.5 weeks

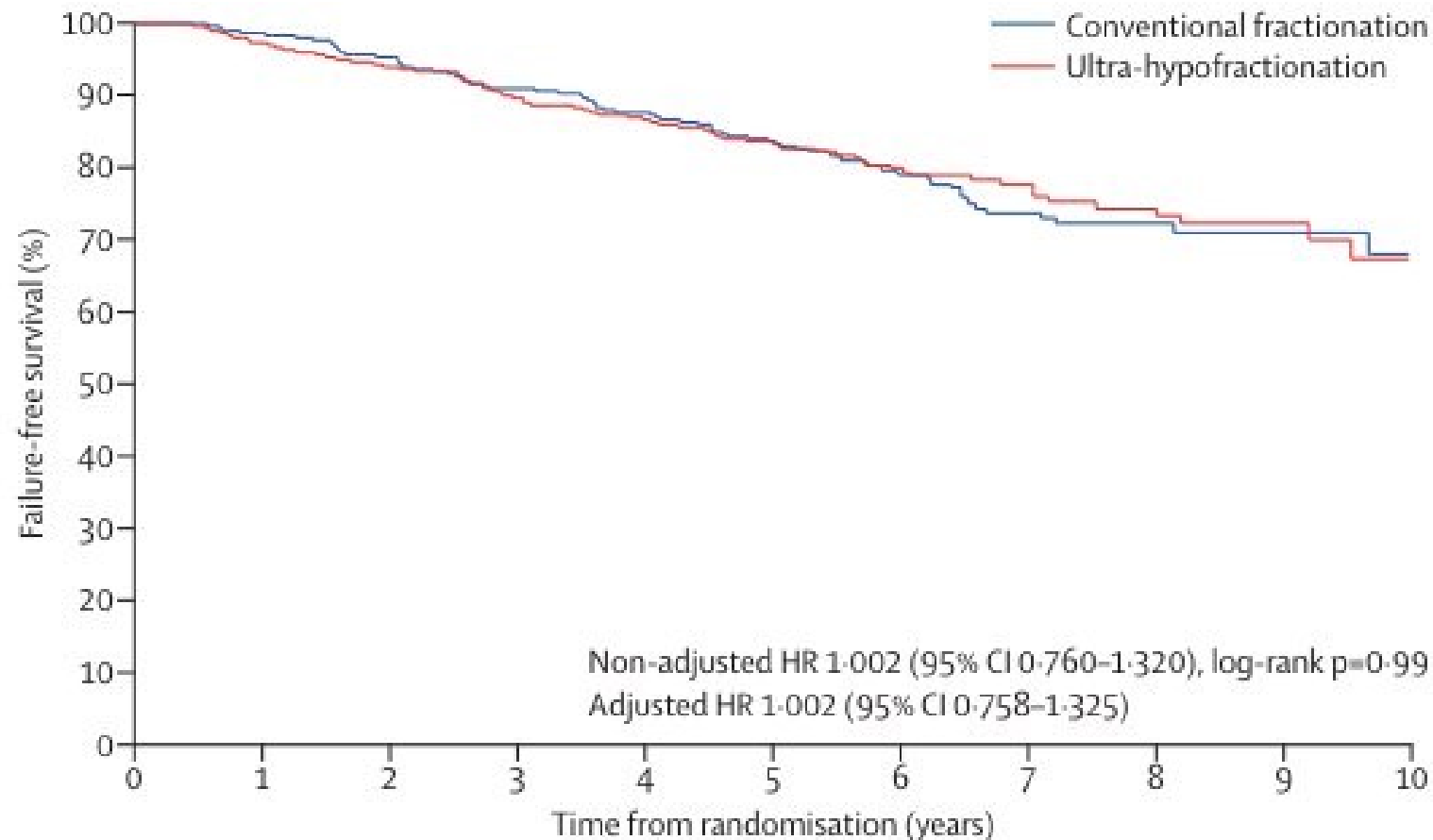
Equieffective for late normal tissue complication probability ($\alpha/\beta=3 \text{ Gy}$)

*T1c-T3a, PSA ≤ 20 with one or two of the following risk factors; T3a or Gleason ≥ 7 or PSA > 10

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial



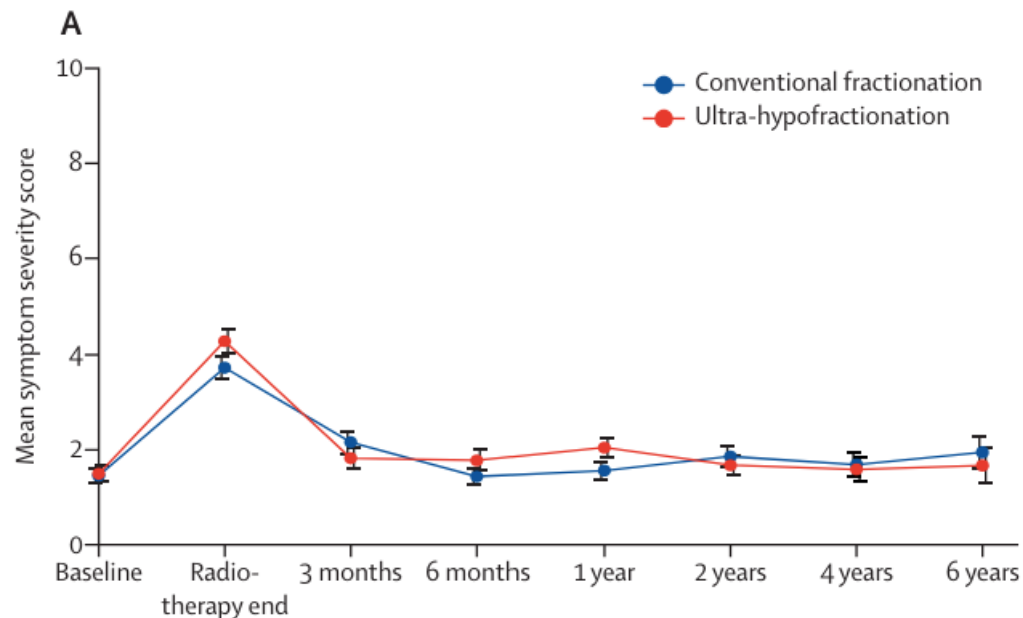
Lancet 2019; 394: 385-95



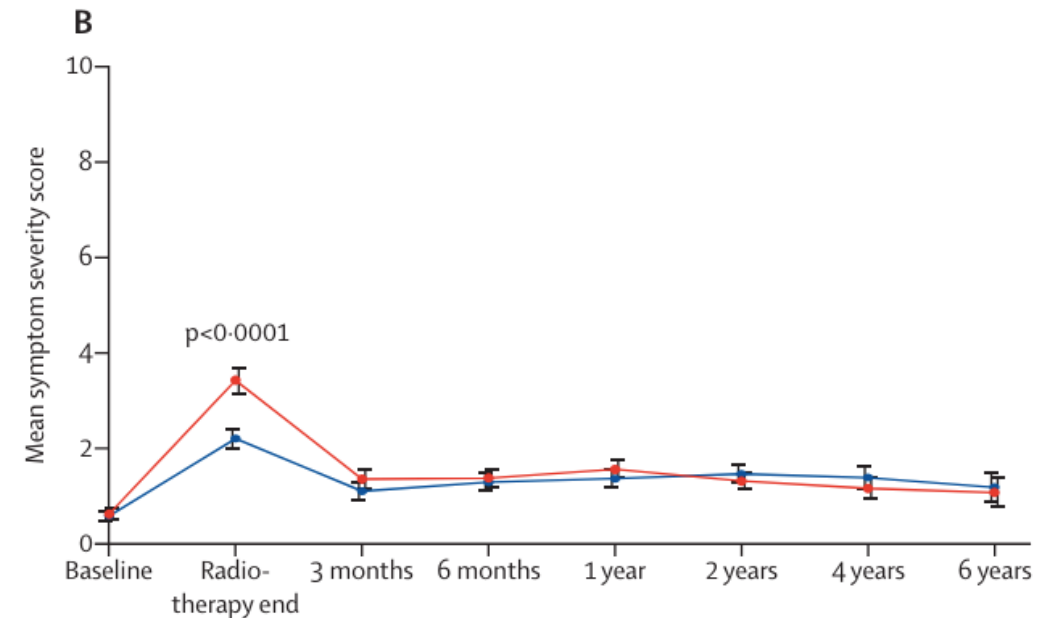
Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial



Lancet Oncol 2021; 22: 235-45

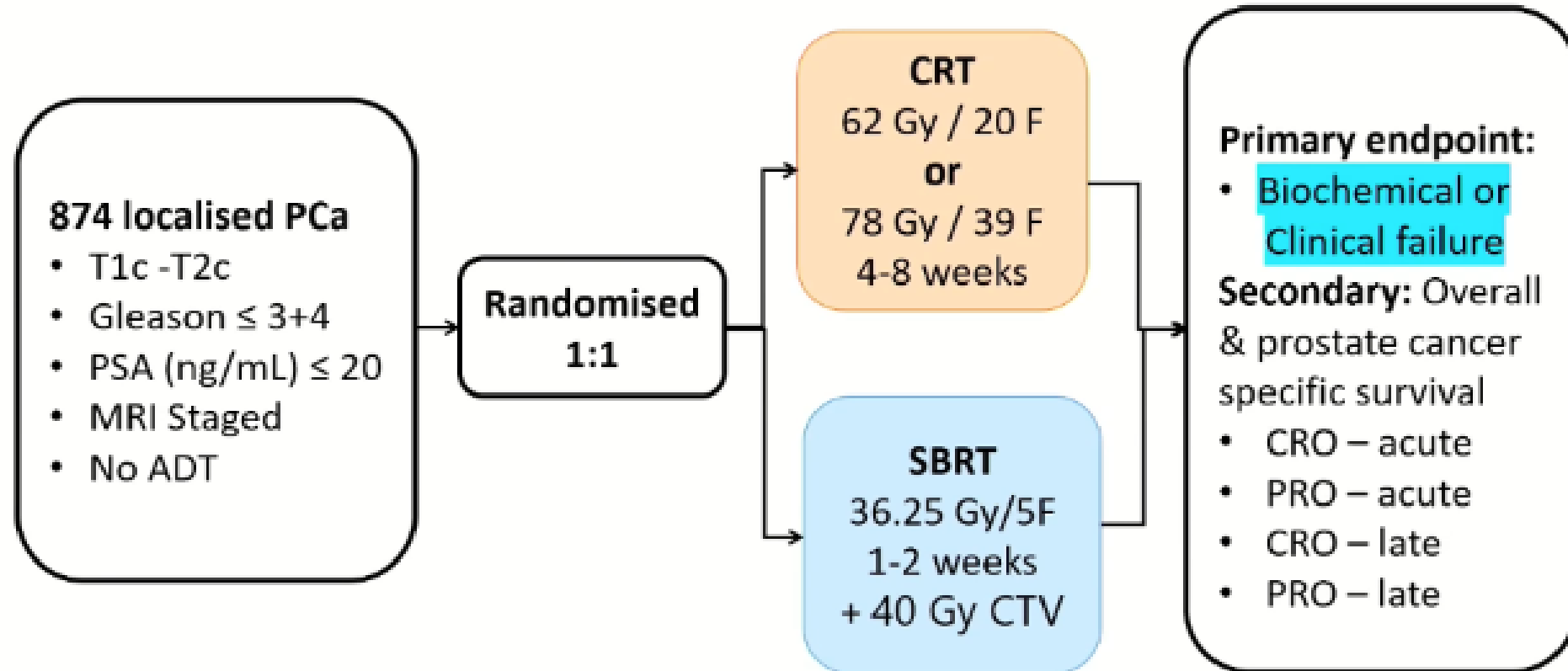


Urinary toxicity

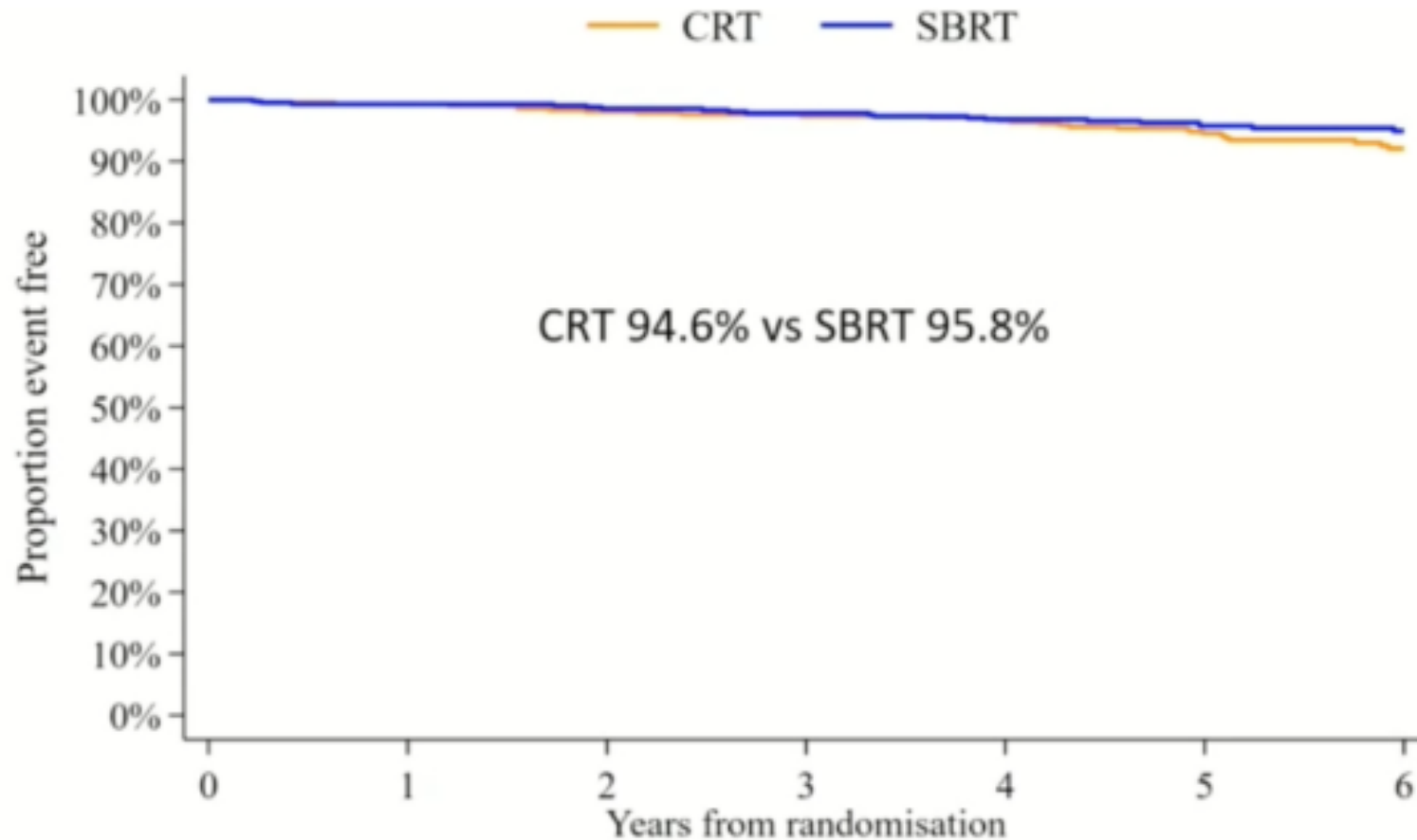


Bowel toxicity

ASTRO 2023: 5-Year Outcomes from PACE B: An International Phase III Randomised Controlled Trial Comparing Stereotactic Body Radiotherapy vs Conventionally Fractionated or Moderately Hypofractionated External Beam Radiotherapy for Localized Prostate Cancer

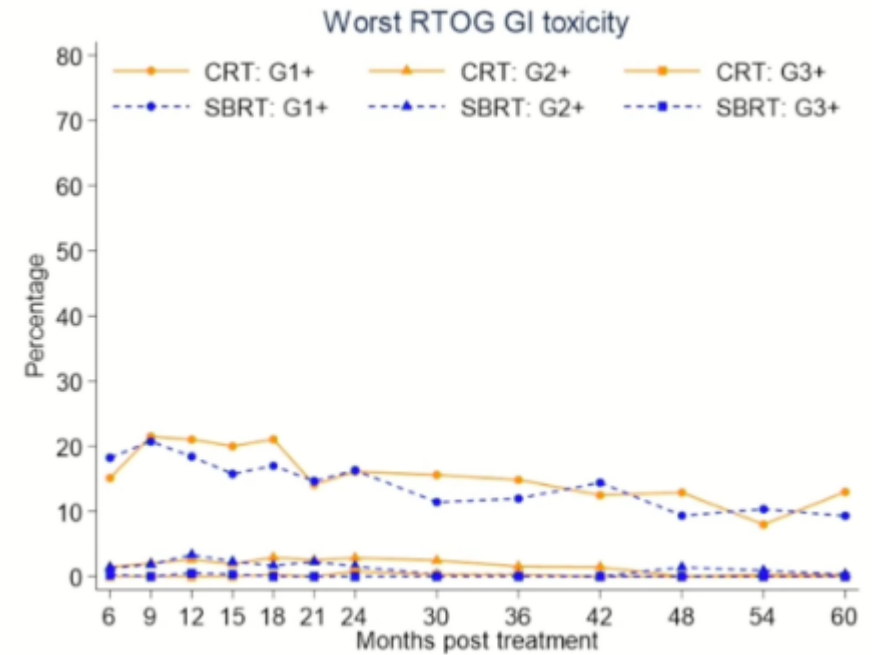
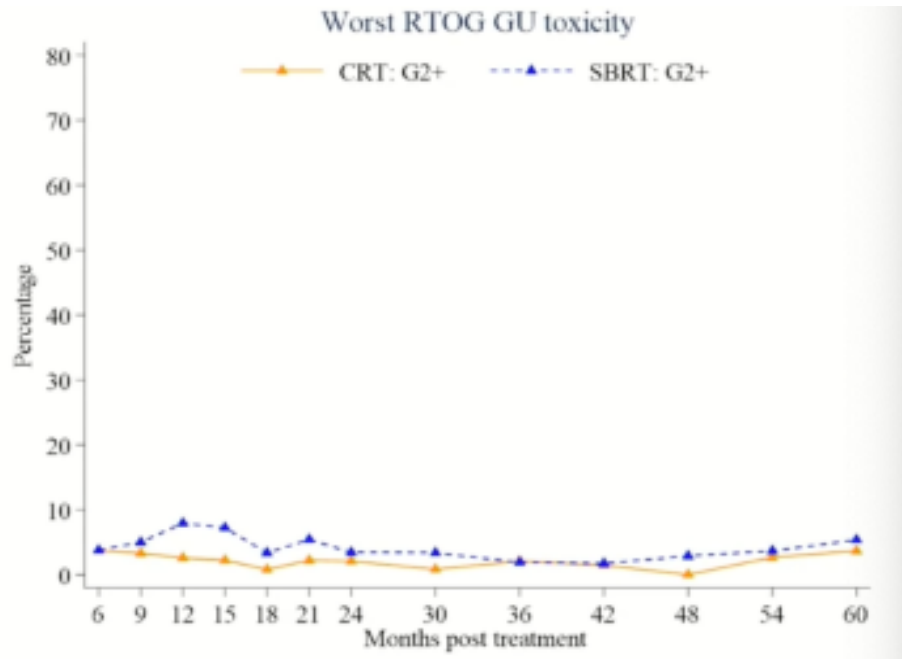


ASTRO 2023: 5-Year Outcomes from PACE B: An International Phase III Randomised Controlled Trial Comparing Stereotactic Body Radiotherapy vs Conventionally Fractionated or Moderately Hypofractionated External Beam Radiotherapy for Localized Prostate Cancer



Biochemical or clinical failure free survival

ASTRO 2023: 5-Year Outcomes from PACE B: An International Phase III Randomised Controlled Trial Comparing Stereotactic Body Radiotherapy vs Conventionally Fractionated or Moderately Hypofractionated External Beam Radiotherapy for Localized Prostate Cancer



RTOG toxicity-up to 5 years

Radioterapia post-operatoria

Recidiva biochimica dopo prostatectomia

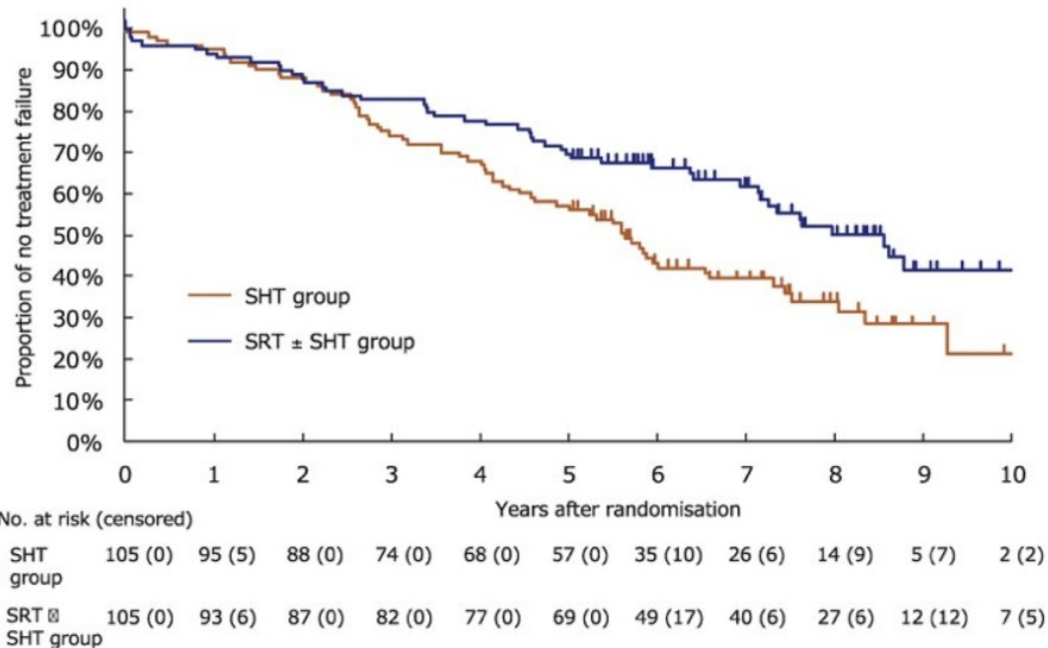
- PSA > 0.2 ng/ml

- 20-40% nell'arco di 10 anni
- La SRT è l'unico trattamento potenzialmente curativo
- La SRT ha dimostrato un vantaggio in BRFS, MFS e CSS

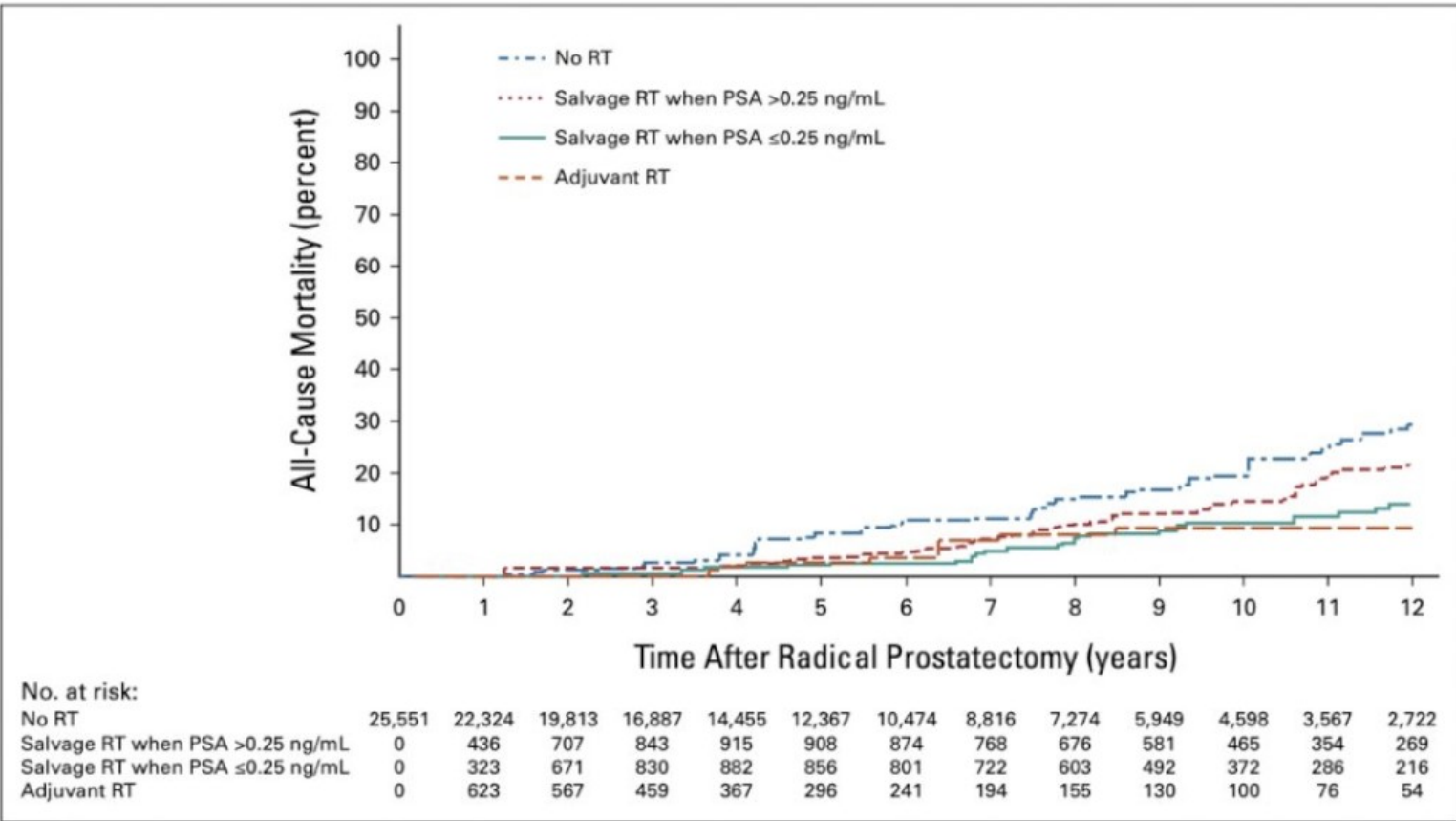
Salvage Radiotherapy Versus Hormone Therapy for Prostate-specific Antigen Failure After Radical Prostatectomy: A Randomised, Multicentre, Open-label, Phase 3 Trial (JCOG0401)



	SHT group	SRT ± SHT group
Percentage of 5-yr freedom from treatment failure of BCL (95% CI)	57% (47–66%)	70% (60–78%)
Median TTF, yr (95% CI)	5.6 (4.5–6.6)	8.6 (7.2–NE)



Prostate-Specific Antigen Level at the Time of Salvage Therapy After Radical Prostatectomy for Prostate Cancer and the Risk of Death



No RT
 SRT PSA > 0.25
 SRT PSA ≤ 0.25
 ART

PSA < 0.25 ng/ml --> ↑ outcome

PET PSMA

Positive scans according to postoperative PSA:

<0.2	33%
0.2-0.49	45%
0.5-0.99	60%
1-1.99	75%
>2	95%

Limitazioni per valori di PSA bassi!!!

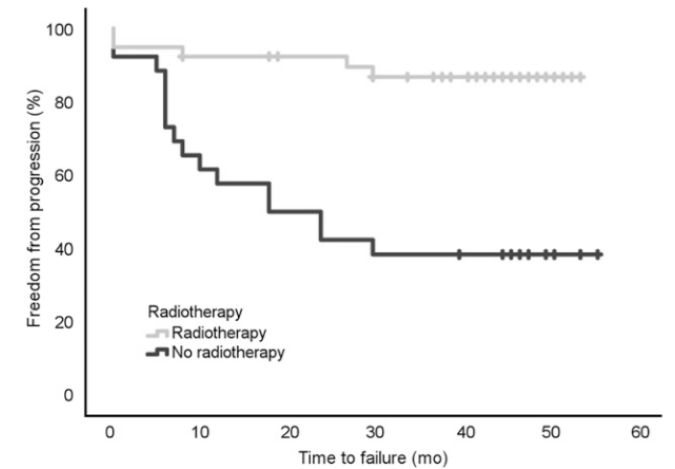
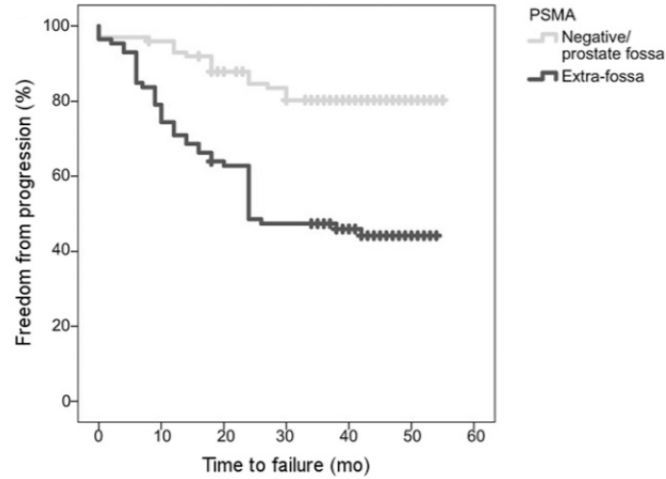
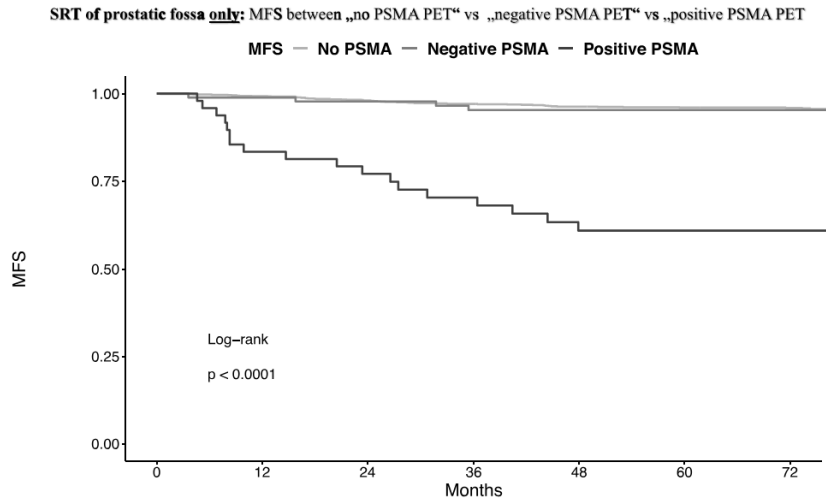
**Negative
PSMA-PET**

no (PSMA-expressing)
cancer cells

$\leq 10^7$ cells,
~microscopic disease



PET PSMA



Guidelines

A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.

Radioterapia post-operatoria ipofrazionata?

JAMA Oncology

RCT: Noninferiority of Hypofractionated vs Conventional Postprostatectomy Radiotherapy for Genitourinary and Gastrointestinal Symptoms

POPULATION

296 Males



Patients with detectable prostate-specific antigen (PSA) after prostatectomy with pT2 with

INTERVENTION

296 Patients randomized



144 Hypofractionated postprostatectomy radiotherapy (HYPOR)

62.5 Gy in 25 fractions

152 Conventionally fractionated postprostatectomy (COPOR)

66.6 Gy in 37 fractions

FINDINGS

There were no statistically significant differences in urinary and bowel change scores between HYPOR and COPOR arms at 2 y



Mean (SD) urinary domain score:

HYPOR, -5.01 (15.10) and COPOR, -4.07 (14.67); $P = .98$

Mean (SD) bowel domain score:

HYPOR, -4.17 (10.97) and COPOR, -1.41 (8.32); $P = .99$

Nessuna differenza statisticamente significativa a 2 anni in tossicità urinaria e intestinale

SE



and Canada

Post-Prostatectomy Ablative-Radiation Therapy. POPART TRIAL

-Protocollo di studio osservazionale

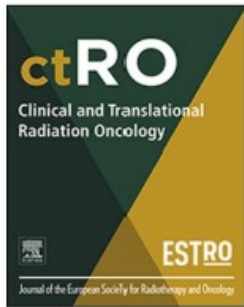
-Centro principale: IRCCS San Gerardo dei Tintori, Monza (Prof. Stefano Arcangeli)

-Radioterapia adiuvante o di salvataggio in **5 frazioni** anziché in 35 frazioni (trattamento convenzionale)



Toxicity profile and Patient-Reported outcomes following salvage Stereotactic Ablative Radiation Therapy to the prostate Bed: The POPART multicentric prospective study

Federica Ferrario ^{a,b,1}, Ciro Franzese ^{c,d,1}, Valeria Faccenda ^e, Suela Vukcaj ^f, Maria Belmonte ^{a,b}, Raffaella Lucchini ^{a,b}, Davide Baldaccini ^d, Marco Badalamenti ^d, Stefano Andreoli ^g, Denis Panizza ^{a,e,*}, Alessandro Magli ^h, Marta Scorsetti ^{c,d}, Stefano Arcangeli ^{a,b}



**Da aprile 2021 a aprile 2023 arruolati 50 pz.
Follow up mediano 12.2 mesi (3-27 mesi)**

Maximum late toxicity after RT.

	Grade 1	Grade 2	Grade ≥ 3
Late GU toxicity	N (%)	N (%)	N (%)
Hematuria	2 (4 %)	–	–
Urinary incontinence	16 (32 %)	–	–
Urinary tract obstruction	1 (2 %)	–	–
Urinary frequency	3 (6 %)	–	–
Non-infectious Cystitis	1 (2 %)	–	–
Total	23 (46 %)	–	–
Late GI toxicity	N (%)	N (%)	N (%)
Hematochezia	–	–	–
Tenesmus/Proctitis	1 (2 %)	–	–
Fecal Incontinence	–	–	–
Bowel frequency	1 (2 %)	–	–
Total	2 (4 %)	–	–

Median and range of patient-reported QoL using EPIC-CP, ICIQ-SF and IIEF 5.

EPIC-CP	Median (range)	
	Baseline	Last follow-up
Urinary Incontinence	2 (0 – 8)	2 (0 – 8)
Urinary Irritation/Obstruction	1 (0 – 4)	1 (0 – 5)
Bowel Symptoms	0 (0 – 5)	0 (0 – 7)
Sexual Dysfunctions	5 (0 – 12)	5 (0 – 12)
Hormonal Symptoms	0 (0 – 7)	0 (0 – 6)
Quality of Life	9 (0 – 19)	10 (1 – 37)
ICIQ-SF	Median (range)	
	Baseline	Last follow-up
Urinary Incontinence	4 (0 – 13)	2 (0 – 16)
IIEF 5	Median (range)	
	Baseline	Last follow-up
Erectile Function	13 (0 – 25)	10 (0 – 25)

Nessuna tossicità significativa né peggioramento della qualità di vita

Recidiva biochimica dopo RT radicale

- PSA > 2 ng/ml

- 30-50% nell'arco di 10 anni

- 10% hanno solo recidiva locale a livello prostatico →
trattamento locale potenzialmente curativo

A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER)

Covariate-adjusted meta-regression comparing efficacy and toxicity between salvage modalities and radical prostatectomy

	2-yr RFS	5-yr RFS	Severe GU toxicity	Severe GI toxicity
Radical prostatectomy				
Adjusted percent ^a (95% CI)	72% (66–78%)	53% (46–59%)	21% (16%–26%)	1.5% (0.4%–3.2%)
Odds ratio (95% CI)	1.0	1.0	NA	NA
p value	Reference	Reference	Reference	Reference
R ² (%)	0.0	0.0	0.0	0.0
Cryotherapy				
Adjusted percent ^a (95% CI)	66% (59–72%)	57% (49–65%)	15% (8–23%)	0.9% (0.3–1.8%)
Odds ratio (95% CI)	0.74 (0.49–1.12)	1.20 (0.80–1.79)	NA	NA
p value	0.2	0.4	0.2	0.5
R ² (%)	25	0.0	8.2	27
HIFU				
Adjusted percent ^a (95% CI)	52% (45–59%)	46% (37–55%)	23% (17%–30%)	0.8% (0.1%–2.1%)
Odds ratio (95% CI)	0.42 (0.28–0.64)	0.76 (0.48–1.21)	NA	NA
p value	<0.001	0.2	0.5	0.4
R ² (%)	0.0	41	15	22
SBRT				
Adjusted percent ^a (95% CI)	58% (46–69%)	56% (37–73%)	5.6% (1.4–12%)	0.0% (0.0–1.2%)
Odds ratio (95% CI)	0.52 (0.30–0.93)	1.13 (0.50–2.58)	NA	NA
p value	0.03	0.8	<0.001	0.07
R ² (%)	55	4.2	0.00	0.0
HDR				
Adjusted percent ^a (95% CI)	77% (69–83%)	58% (52–64%)	9.6% (6.0–13.9%)	0.0% (0.0–0.3%)
Odds ratio (95% CI)	1.26 (0.77–2.09)	1.25 (0.88–1.78)	NA	NA
p value	0.4	0.2	0.002	0.003
R ² (%)	0.0	91	0.0	0.0
LDR				
Adjusted percent ^a (95% CI)	79% (72–85%)	53% (43–63%)	9.1% (5.2–14%)	2.1% (0.6–4.0%)
Odds ratio (95% CI)	1.49 (0.89–2.50)	1.02 (0.63–1.67)	–	–
p value	0.13	0.9	0.001	0.6
R ² (%)	4.3	5.2	12	20%

Dati a favore della re-RT ma importanti limitazioni !!!!

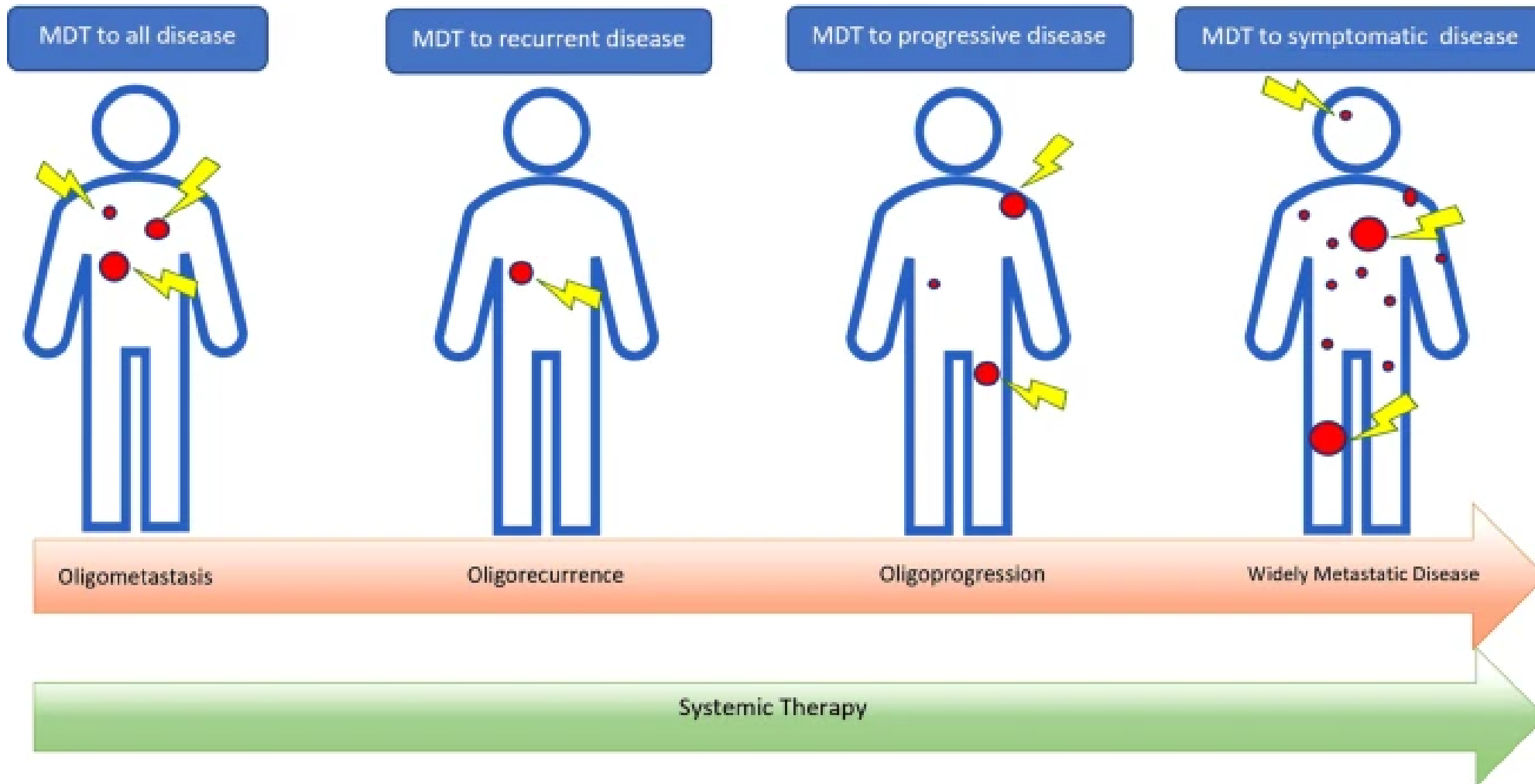


Radioterapia nel paziente metastatico

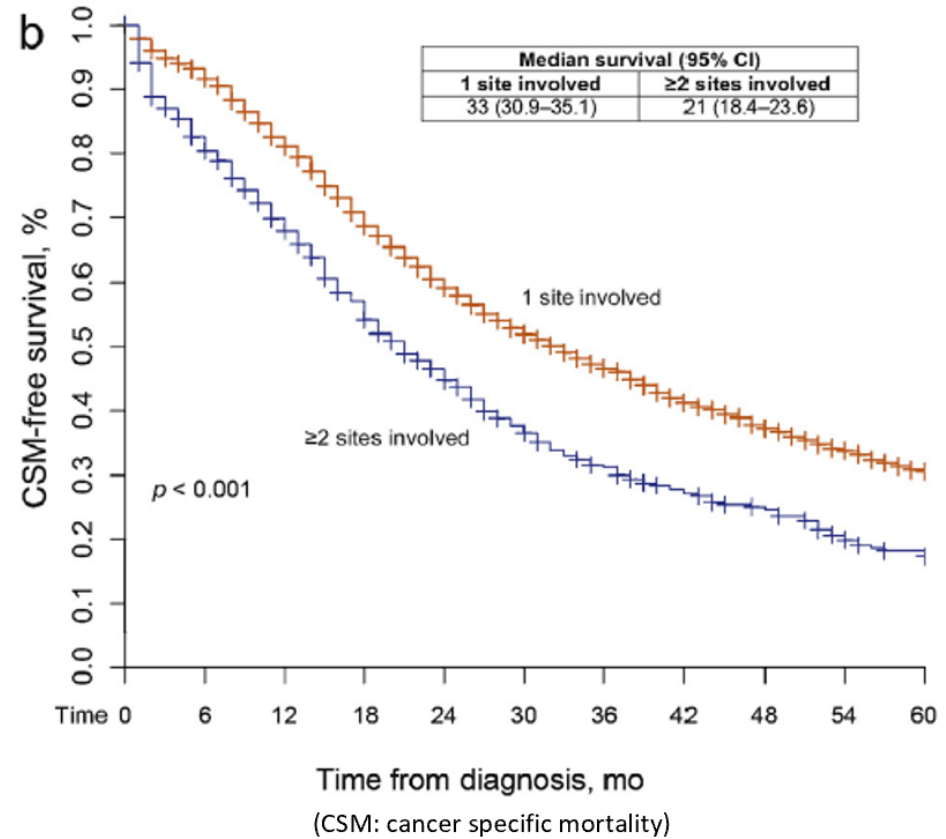
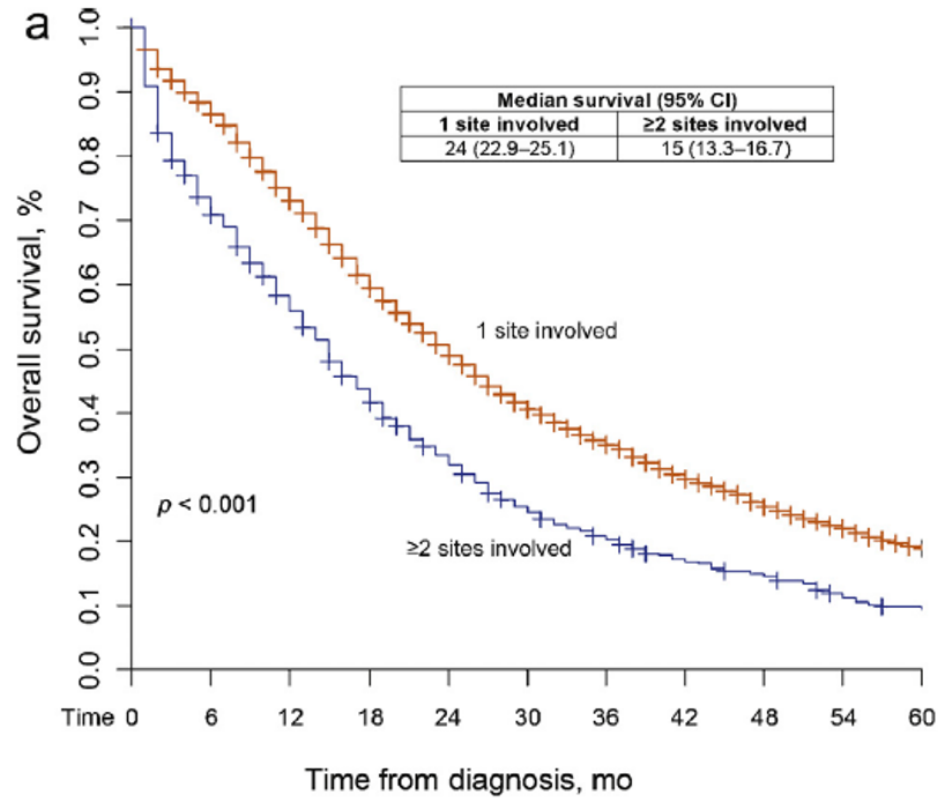
Solo sintomatica?



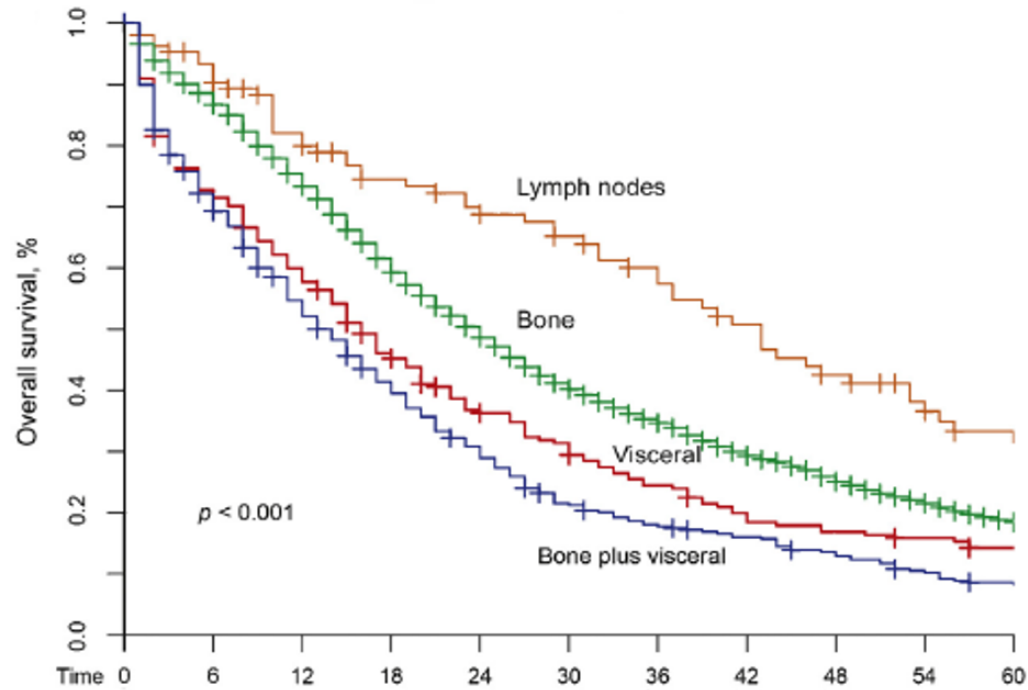
Oligometastatic vs Polymetastatic disease



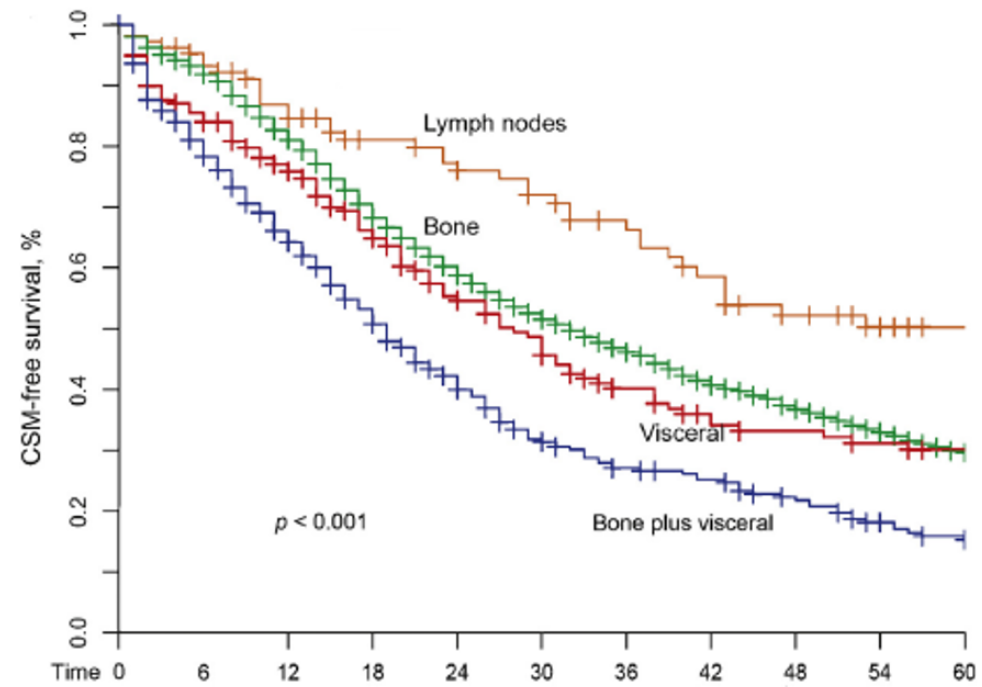
IMPACT OF THE SITE OF M+ ON SURVIVAL IN PATIENTS WITH mPC



IMPACT OF THE SITE OF M+ ON SURVIVAL IN PATIENTS WITH mPC



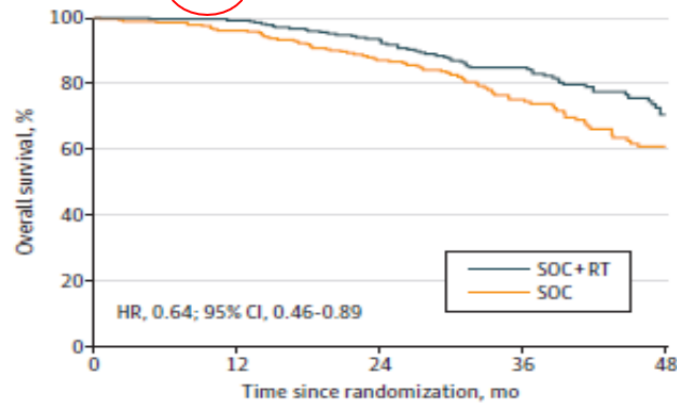
Median survival (95% CI)			
Lymph nodes	bone	visceral	bone plus visceral
43 (35.1–50.9)	24 (22.9–25.1)	16 (12.9–19.1)	14 (12.0–15.9)



Median survival (95% CI)			
Lymph nodes	bone	visceral	bone plus visceral
61 (41.2–80.8)	32 (29.9–34.0)	26 (20.7–29.6)	19 (16.4–20.3)

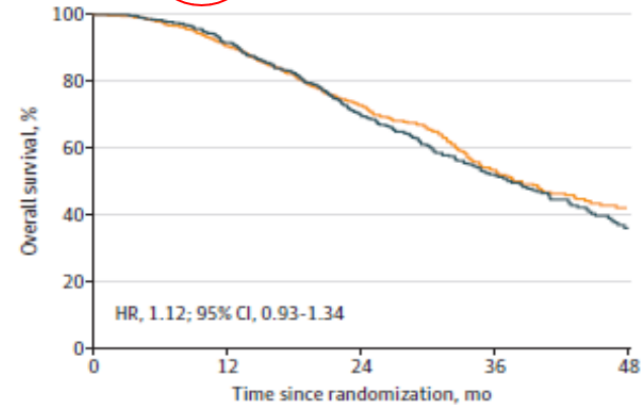
IMPACT OF BONE METASTATIC BURDEN ON SURVIVAL

A Overall survival in ≤ 3 bone metastases (\pm NRLN) subcohort



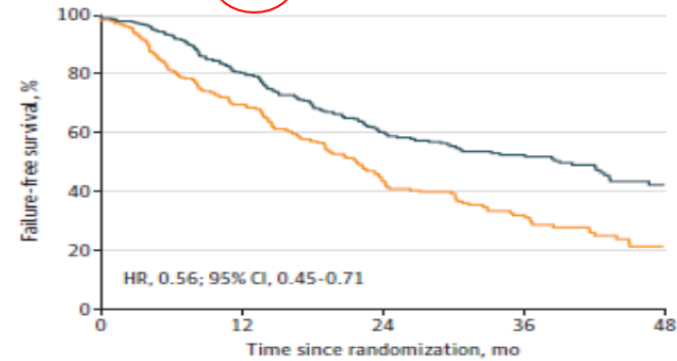
No. at risk (events)		0	12	24	36	48	
SOC	290 (11)	274	(24)	188	(22)	116 (19)	50
SOC+RT	287 (2)	281	(15)	212	(18)	145 (18)	59

C Overall survival in ≥ 4 bone metastases (\pm NRLN) subcohort



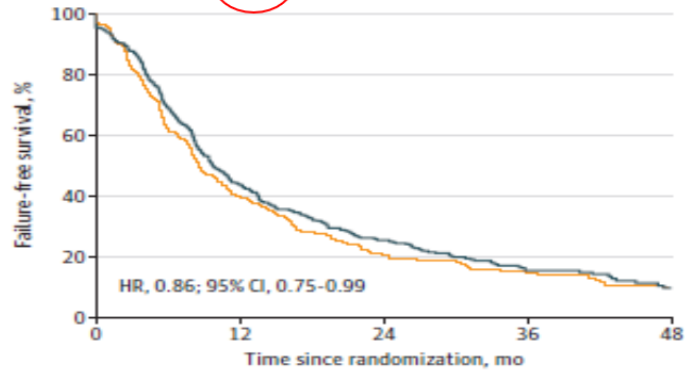
No. at risk (events)		0	12	24	36	48	
SOC	512 (47)	452	(83)	281	(64)	147 (25)	45
SOC+RT	498 (41)	441	(96)	260	(58)	136 (30)	38

B Failure-free survival in ≤ 3 bone metastases (\pm NRLN) subcohort



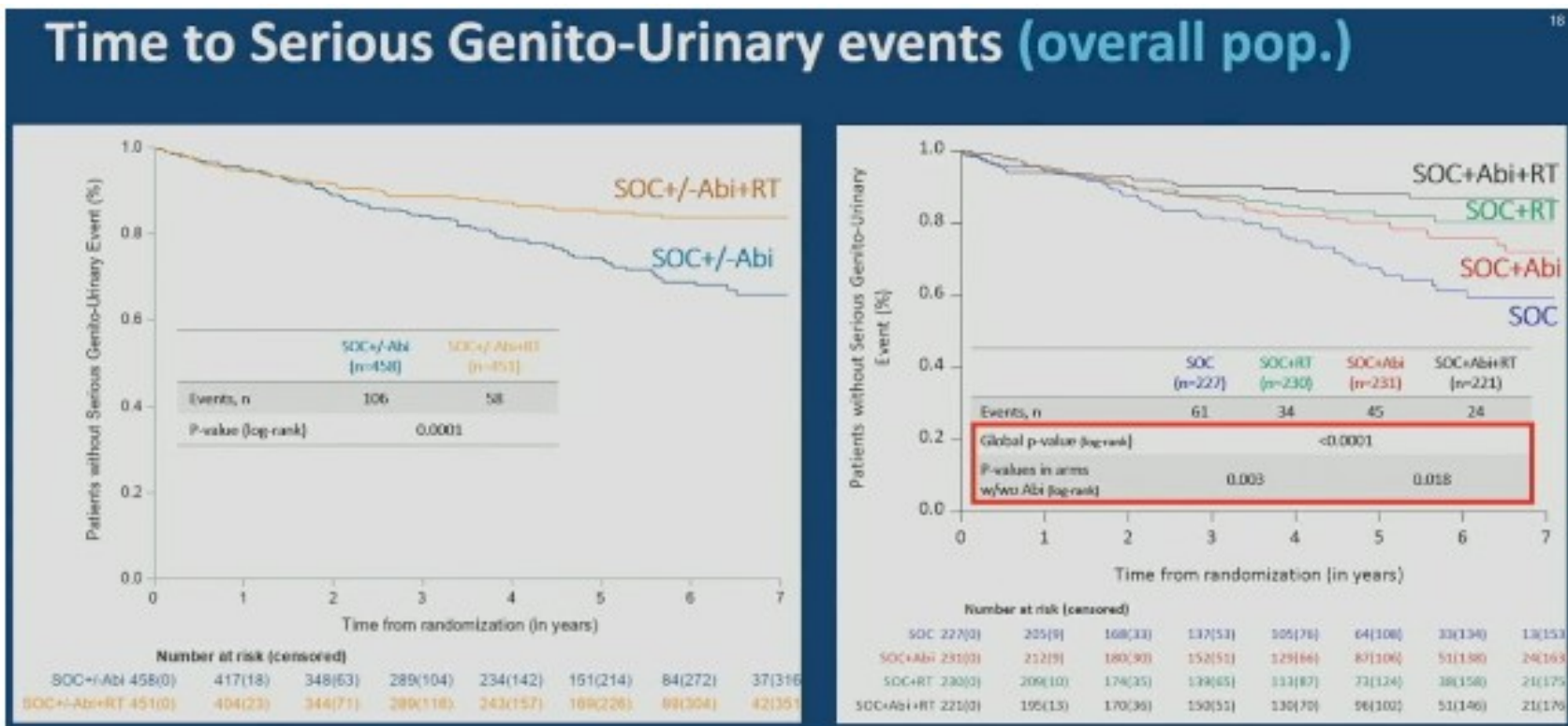
No. at risk (events)		0	12	24	36	48	
SOC	290 (87)	195	(66)	86	(19)	41 (11)	12
SOC+RT	287 (56)	228	(52)	129	(15)	86 (12)	26

D Failure-free survival in ≥ 4 bone metastases (\pm NRLN) subcohort



No. at risk (events)		0	12	24	36	48	
SOC	512 (301)	201	(90)	69	(15)	36 (8)	8
SOC+RT	498 (276)	212	(84)	89	(28)	34 (8)	9

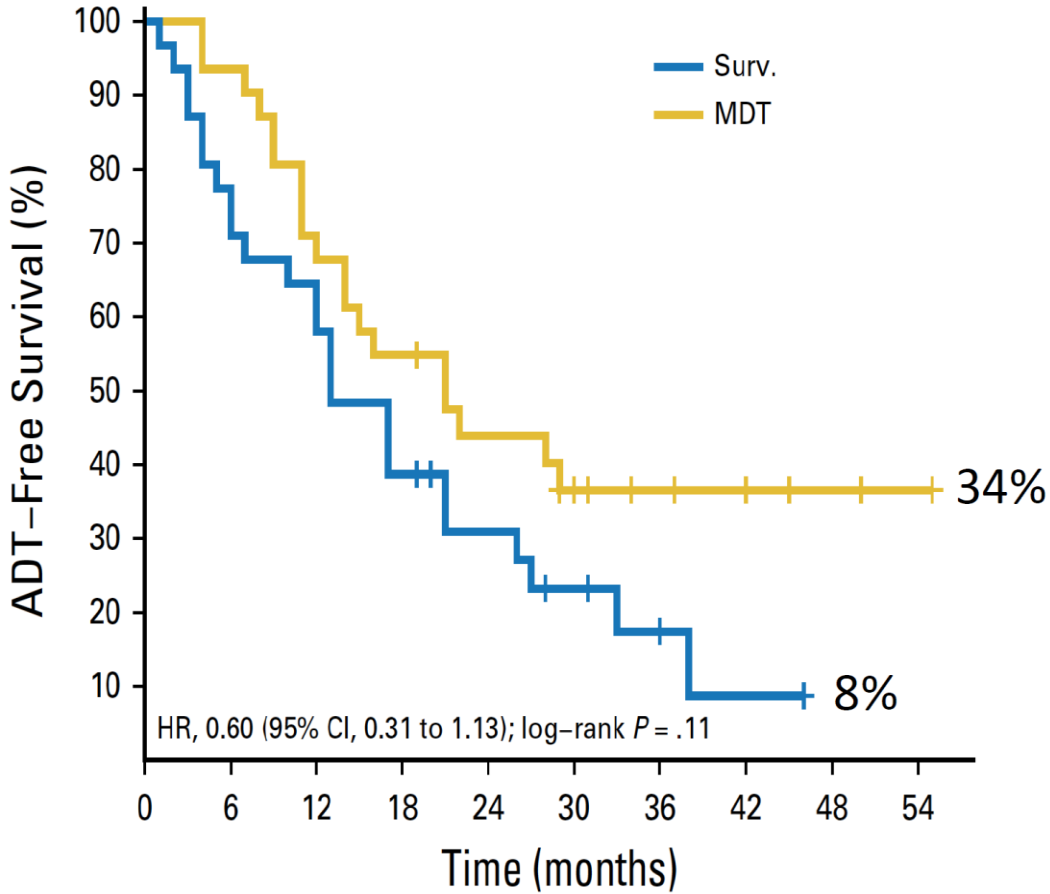
ASCO 2023: Prostate Irradiation in Men with De Novo, Low-Volume, Metastatic, Castration-Sensitive Prostate Cancer (mCSPC): Results of PEACE-1, a Phase 3 Randomized Trial with a 2x2 Design



Local RT prevents serious GU events, irrespectively of the disease burden (low vs high volume)

- Definition of serious GU events:**
- Urinary Catheter
 - Double J Stent
 - Nephrostomy
 - Prostate RT or TURP
 - Radical Prostatectomy

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial



Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer

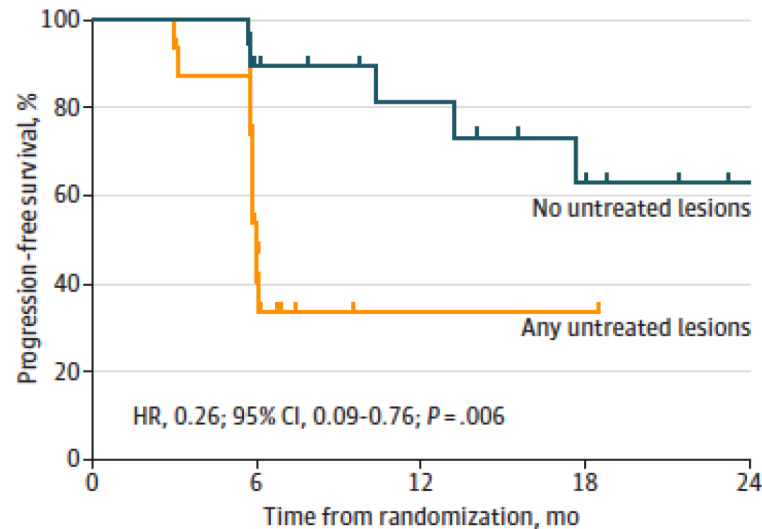
The ORIOLE Phase 2 Randomized Clinical Trial

PSMA-targeted PET-CT after randomization

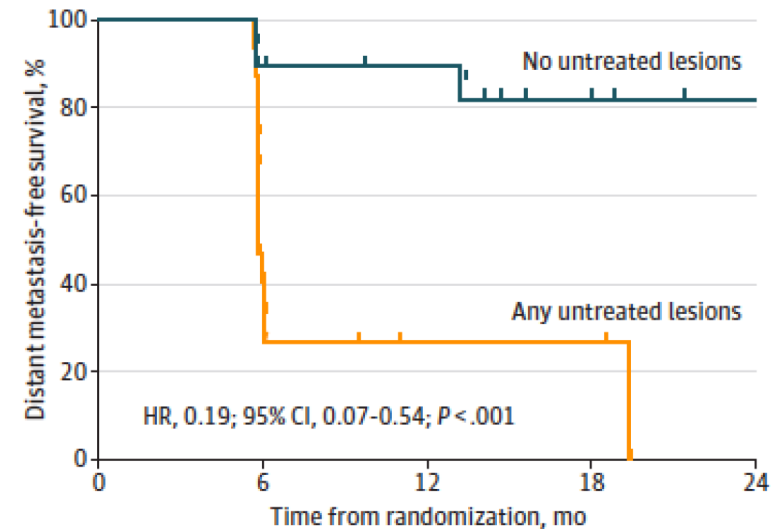


45% had lesions not included in RT fields

C PFS stratified by presence of untreated lesions

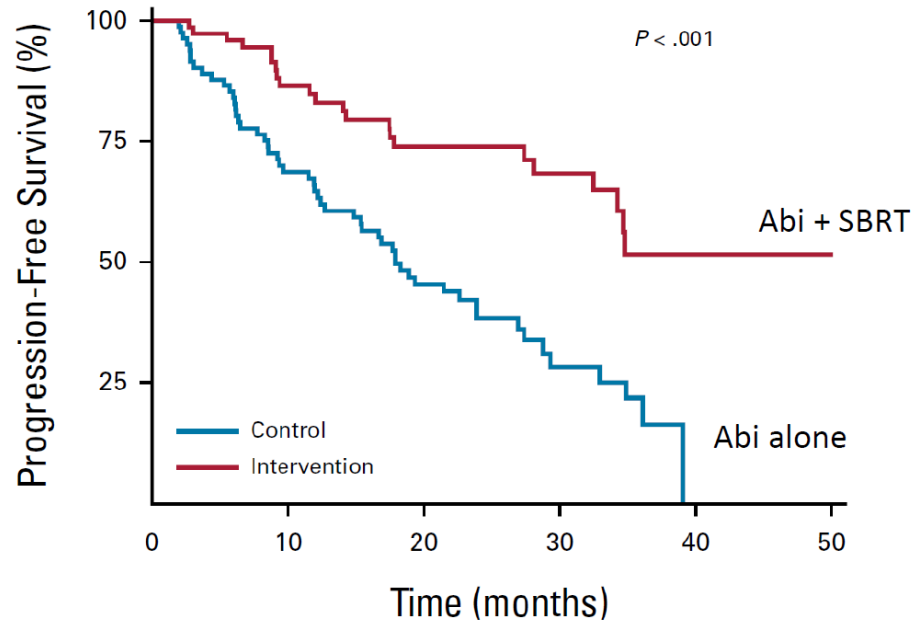


D DMFS stratified by presence of untreated lesions

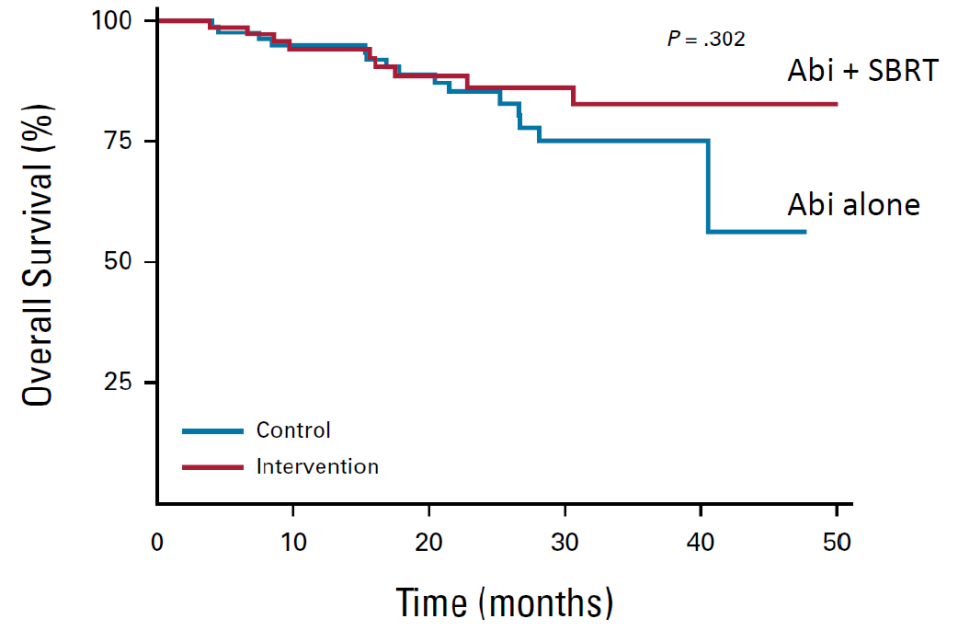


ARTO Trial

A



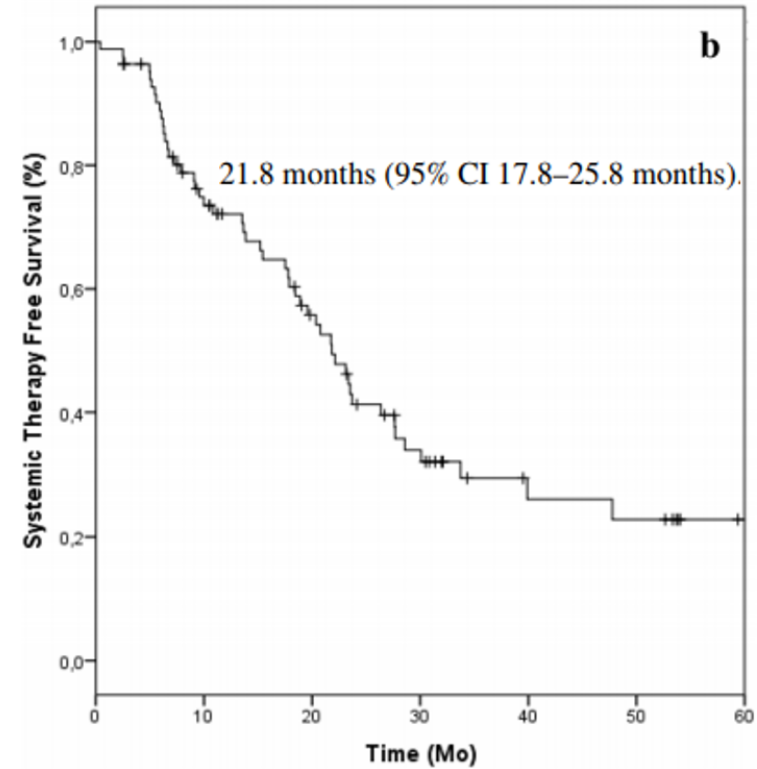
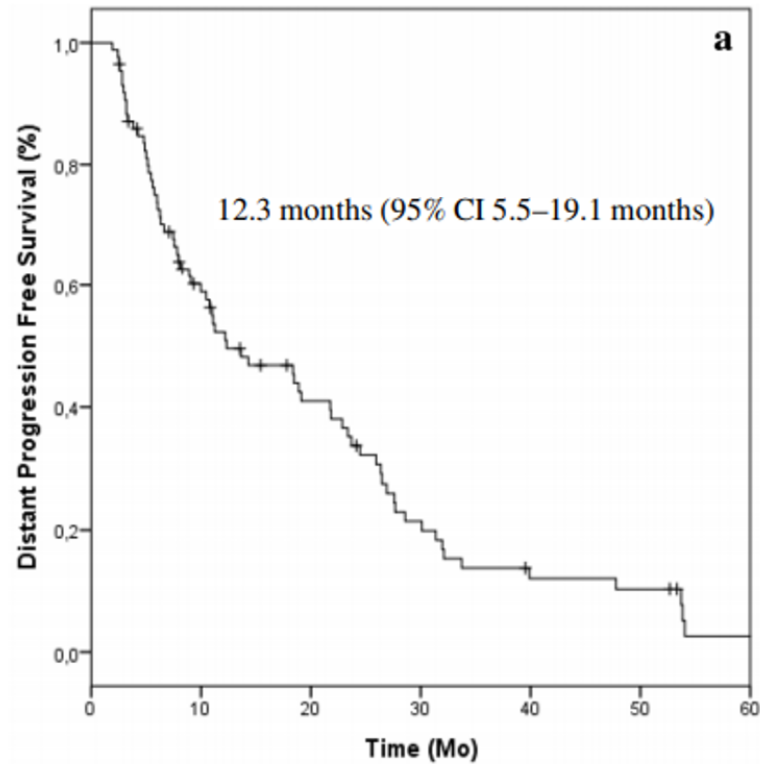
B



- **PSA response: 68.3% Abi vs 92% Abi + SBRT**
- **Complete PSA response: 23.2% Abi vs 56% Abi + SBRT**

MDT improves biochemical response and PFS in oligoprogressive mCRPC patients

OLIGOPROGRESSIVE DISEASE



The beginning of the second-line systemic therapies can be postponed by SBRT for almost 2 years



- ✓ La radioterapia ipofrazionata nel tumore della prostata è uno standard terapeutico
- ✓ SBRT è un trattamento fattibile ed efficace sia sul tumore primitivo che nelle sedi metastatiche
- ✓ La reirradiazione può essere fattibile in pazienti selezionati