Radioterapia del tumore primitivo nel carcinoma prostatico metastatico ed integrazione con la terapia sistemica: a chi, come e quando?

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Nessun conflitto di interesse da dichiarare

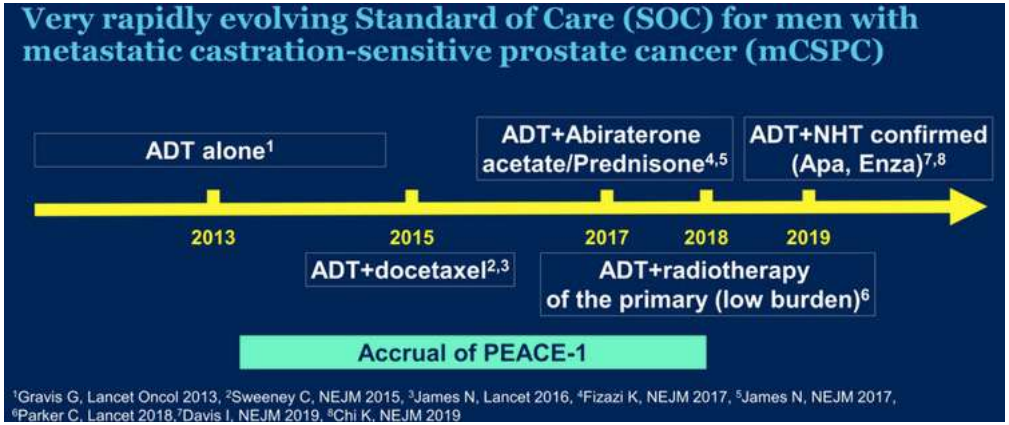
AGENDA

- Razionale
- Setting
- Letteratura
- Studi in corso
- Pitfalls
- Conclusioni

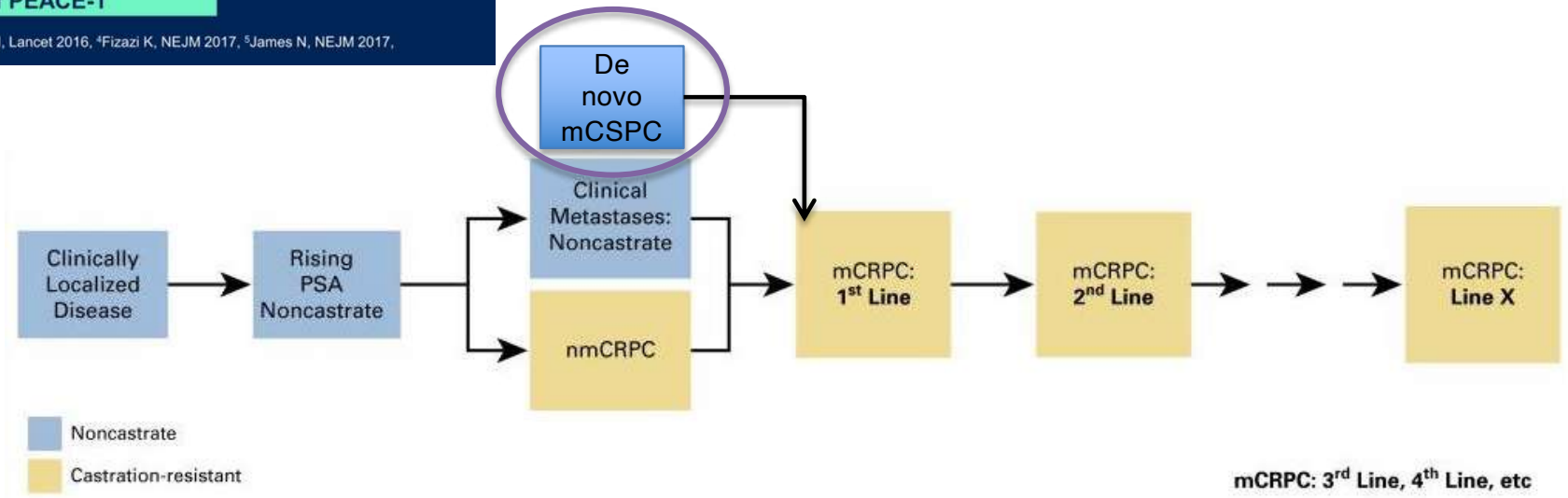
RAZIONALE

- STORICO – "*proof of principle*": altri distretti (rene, colon)
- RADIOBIOLOGICO: tumor self-seeding, abscopal effect
- CLINICO: incremento del controllo locale e riduzione della necessità di trattamento palliativo; eradicazione di malattia con potenziale di metastatizzazione; miglior risposta ad ADT
- DI OPPORTUNITÀ: nuovi farmaci e miglior outcome
- MEDICINA PERSONALIZZATA

QUALE SETTING



- Sincrono✓ vs metacrono
- mCSPC✓ vs mCRPC
- "Curativo"✓ vs Palliativo



STUDI RETROSPETTIVI

Might Men Diagnosed with Metastatic Prostate Cancer Benefit from Definitive Treatment of the Primary Tumor? A SEER-Based Study

Stephen H. Culp[a,*], *Paul F. Schellhammer*[b], *Michael B. Williams*[b]

PLOS ONE

Identifying Optimal Candidates for Local Treatment of the Primary Tumor Among Patients Diagnosed with Metastatic Prostate Cancer: A SEER-based Study

Nicola Fossati[a,b], *Quoc-Dien Trinh*[c], *Jesse Sammon*[d], *Akshay Sood*[d], *Alessandro Larcher*[b,e], *Maxine Sun*[e], *Pierre Karakiewicz*[e], *Giorgio Guazzoni*[b], *Francesco Montorsi*[b], *Alberto Briganti*[b], *Mani Menon*[d], *Firas Abdollah*[d,*]

RESEARCH ARTICLE

Does Radiotherapy for the Primary Tumor Benefit Prostate Cancer Patients with Distant Metastasis at Initial Diagnosis?

Yeona Cho[1], Jee Suk Chang[1], Koon Ho Rha[2], Sung Joon Hong[2], Young Deuk Choi[2], Won Sik Ham[2], Jun Won Kim[1], Jaeho Cho[1]*

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer

Chad G. Rusthoven, Bernard L. Jones, Thomas W. Flaig, E. David Crawford, Matthew Koshy, David J. Sher, Usama Mahmood, Ronald C. Chen, Brian F. Chapin, Brian D. Kavanagh, and Thomas J. Pugh

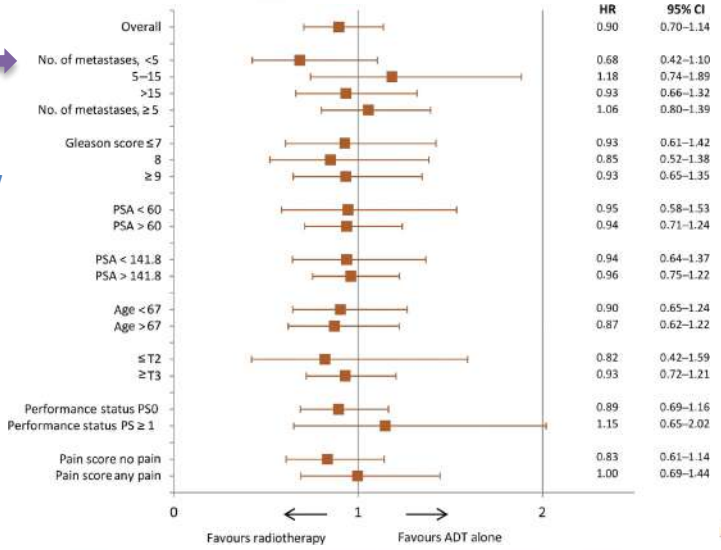
STUDI PROSPETTICI 1

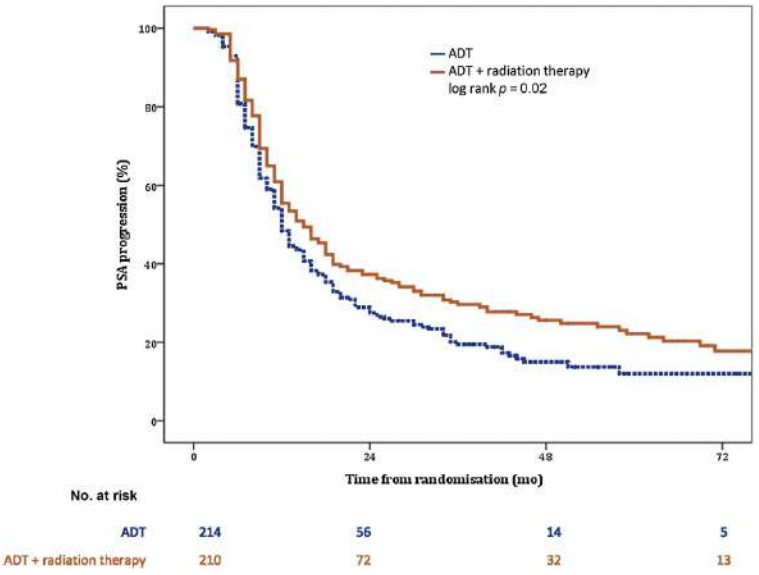
Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial

Liselotte M.S. Boevé[a,b,], Maarten C.C.M. Hulshof[c], André N. Vis[b], Aeilko H. Zwinderman[d], Jos W.R. Twisk[e], Wim P.J. Witjes[f], Karl P.J. Delaere[g], R. Jeroen A. van Moorselaar[b], Paul C.M.S. Verhagen[h], George van Andel[a]*

- ✧ Dose
- ✧ No stratificazione
- ✧ Stadiazione
- ✧ Tp sistemica obsoleta

70 Gy/35 fx/7w o 57.76 Gy/19 fx/6w





432 PTS (216+216)
FU 47 mo (36-68)
OS 45 vs 43 mo (NS)
mTTPP 15 vs 12 mo (p=0.02). aHR NS

STUDI PROSPETTICI 2

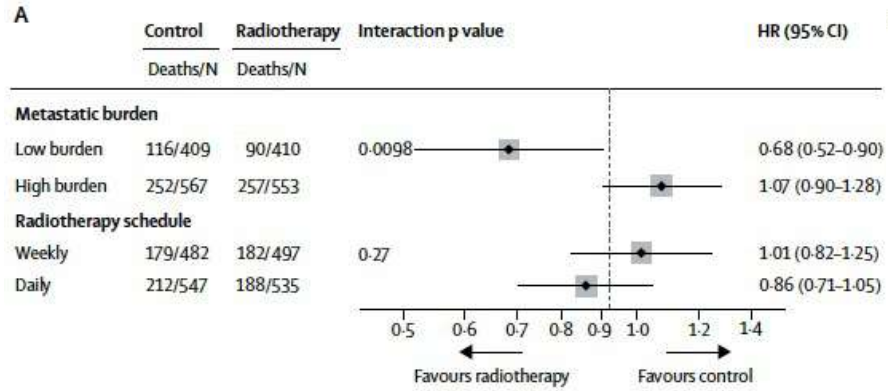
- ✧ Stratificazione a posteriori
- ✧ RT non a tutti, dose
- ✧ mOS>mFU -> eventi tardivi sintomatici
- ✧ Tp sistemica obsoleta
- ✧ Stadiazione convenzionale

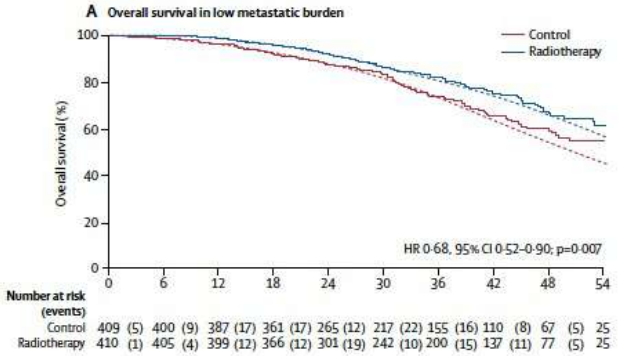
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

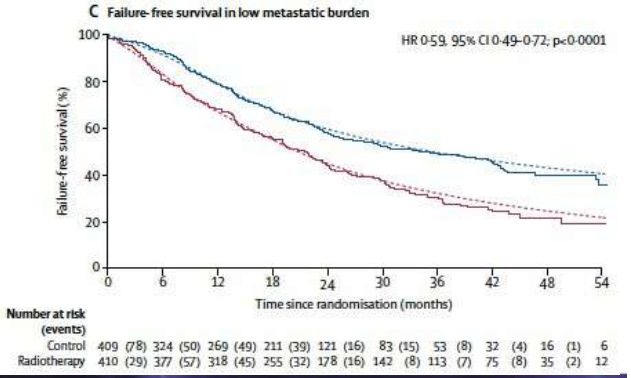
Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar*, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†

55 Gy/20 fx/4w vs 36 Gy/6 fx/6w

2061 pts (1029+1032)
18% Docetaxel
40% low met burden
mFU 37 mo
mOS 46 vs 48 mo (3y 62 vs 65%), NS
LMB: 3yOS 73 vs 81% (p=0.007)
mFFS 13 vs 17 mo (3y 23 vs 32%) (p<0.0001)





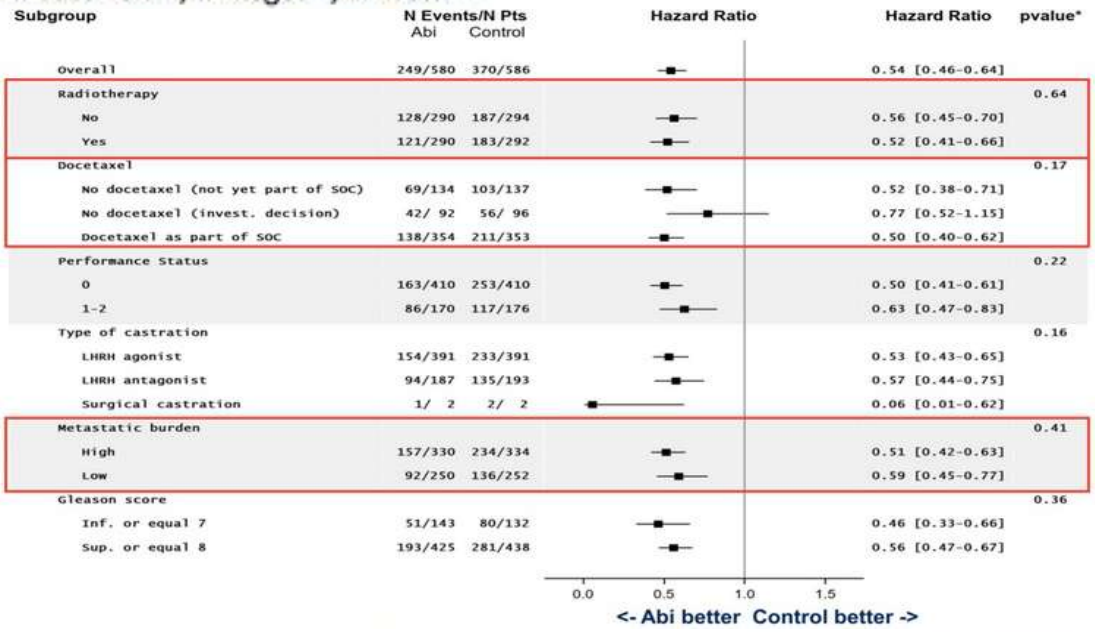


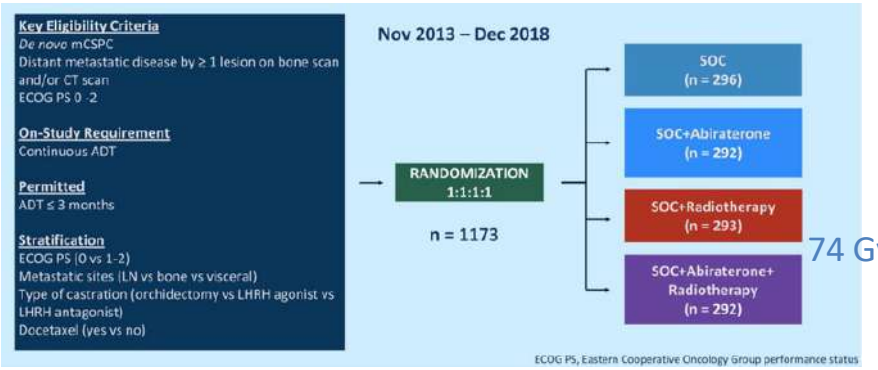
STUDI PROSPETTICI 3

1173 pts
mFU 4.4 ys
rPFS HR 0.5 (p<0.0001)
OS NO D 5.7 vs 4.7 ys (HR 0.83, p=0.034)
OS D NR vs 4.4 ys (HR 0.75, p=0.021)

LBA5 **A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: Overall survival with abiraterone acetate plus prednisone in PEACE-1**

K. Fizazi[1], J. Carles Galceran[2], S. Foulon[1], G. Roubaud[3], R. McDermott[4], A. Fléchon[5], B. Tombal[6], S. Supiot[7], D.R. Berthold[8], P. Ronchin[9], G. Kacso[10], G. Gravis Mescam[11], F. Calabro[12], J.F. Berdah[13], A. Hasbini[14], M. Silva[15], A. Thiery-Vuillemin[16], I. Latorzeff[17], I. Rieger[18], A. Bossi[19]





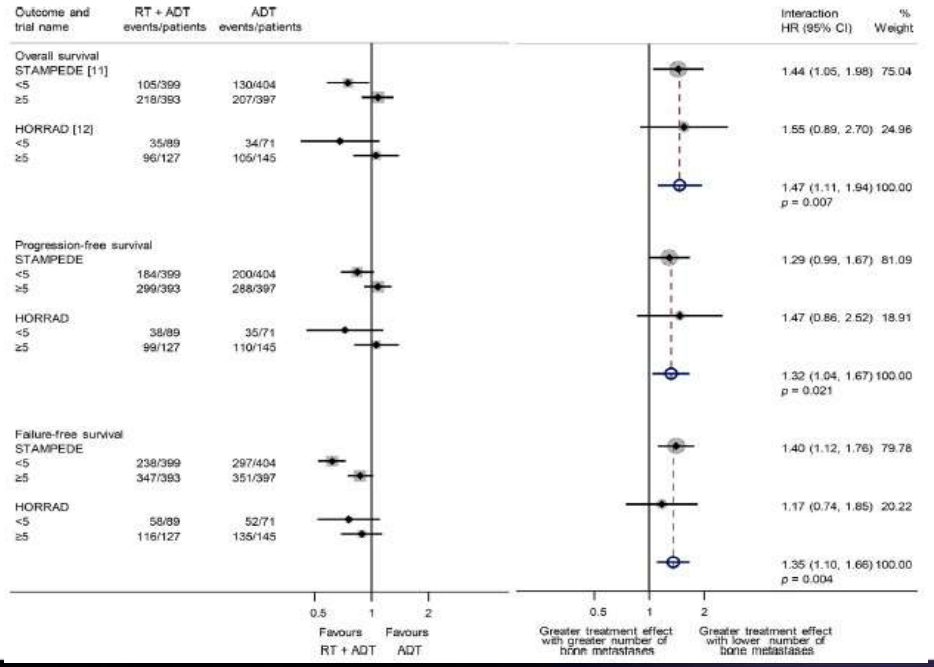
74 Gy/37 fx

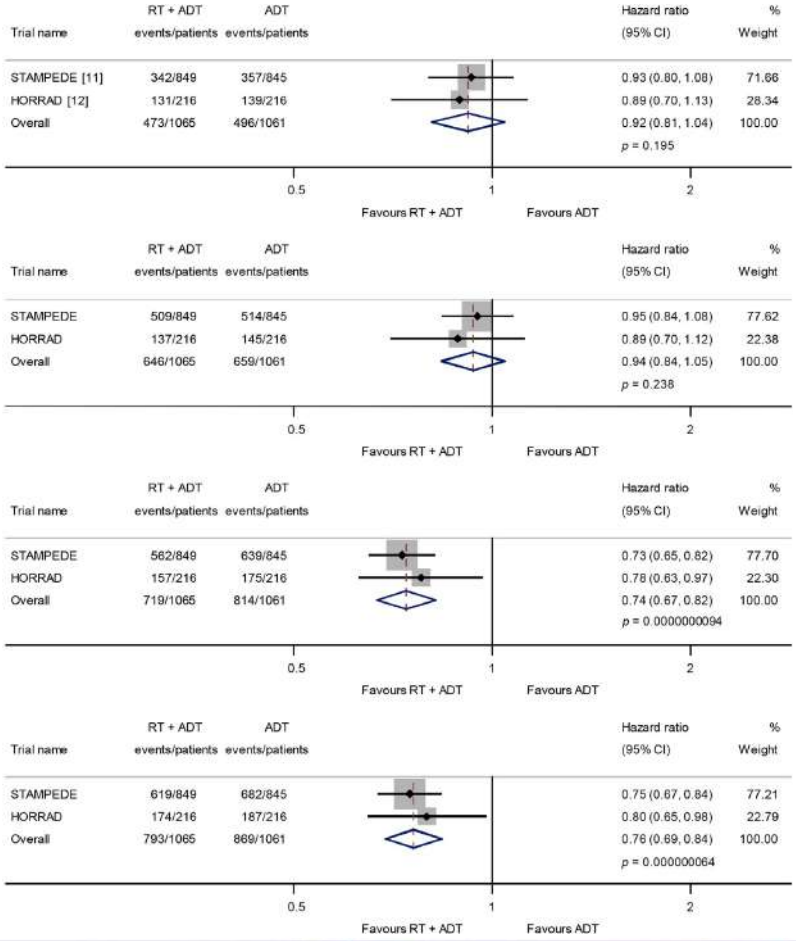
		SOC (+/- RXT) (n = 589)	SOC (+/- RXT) + Abiraterone (n = 583)
Median age, year (IQR)		66 (59–72)	67 (61–72)
ECOG PS score, n (%)	0 1-2	412 (70) 177 (30)	412 (71) 171 (29)
Gleason score at initial diagnosis, n (%)	≤ 7 ≥ 8	132 (23) 440 (77)	144 (25) 427 (75)
Median time from diagnosis, month (IQR)		2.3 (1.5-3.1)	2.3 (1.6-3.2)
Metastatic sites, n (%)	Lymph nodes only Bone without visceral Visceral	52 (9) 475 (81) 62 (11)	47 (8) 472 (81) 64 (11)
Disease burden, n (%)	Low High	252 (43) 334 (57)	250 (43) 330 (57)
Median baseline PSA, ng/mL (IQR)		11.4 (3.1-55.3)	14.2 (3.2-62.1)
Docetaxel, n (%)	Yes No	355 (60) 234 (40)	355 (61) 228 (39)

METANALISI

Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis

Sarah Burdett [a,], Liselotte M. Boevé [b,c,†], Fiona C. Ingleby [d,†], David J. Fisher [a], Larysa H. Rydzewska [a], Claire L. Vale [a], George van Andel [c], Noel W. Clarke [e], Maarten C. Hulshof [f], Nicholas D. James [g], Christopher C. Parker [h], Mahesh K. Parmar [d], Christopher J. Sweeney [i], Matthew R. Sydes [d], Bertrand Tombal [j], Paul C. Verhagen [k], Jayne F. Tierney [a], the STOPCAP M1 Radiotherapy Collaborators*





LINEE GUIDA

SYSTEMIC THERAPY FOR CASTRATION-NAÏVE PROSTATE CANCER[oo]

M0[pp,qq] → Monitoring (preferred) or ADT[t,rr]

M1[ss,tt,uu,vv,ww] → ADT[t] with one of the following:
- Preferred regimens:
  - Abiraterone (category 1)[t,ff]
  - Apalutamide (category 1)[t]
  - Docetaxel 75 mg/m^2 for 6 cycles[xx] (category 1)[yy]
  - Enzalutamide (category 1)[t]
- EBRT[o] to the primary tumor for low-volume M1[xx] or ADT[t,rr]

→ • Physical exam + PSA every 3–6 mo
• Imaging for symptoms[g]
• Consider periodic imaging to monitor treatment response[g]

→ Progression[j,kk,zz]

- Studies negative for distant metastases → See Systemic Therapy for M0 CRPC (PROS-13)
- Studies positive for distant metastases → See Systemic Therapy for M1 CRPC (PROS-14)

[g] See Principles of Imaging (PROS-D).

[j] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.

[o] See Principles of Radiation Therapy (PROS-F).

[t] See Principles of Androgen Deprivation Therapy (PROS-H).

[ff] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option).

[kk] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 PSMA-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging. Soft tissue imaging of pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-D).

[oo] The term "castration-naïve" is used to define patients who have not been treated with ADT and those who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naïve" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

[pp] PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease.

[qq] Patients with a life expectancy ≤5 years can consider observation. See Principles of Active Surveillance and Observation (PROS-E).

[rr] Intermittent ADT can be considered for patients with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-H).

[ss] EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.

[tt] ADT alone (see PROS-H) or observation are recommended for asymptomatic patients with metastatic disease and life expectancy ≤5 years.

[uu] Tumor and germline testing for homologous recombination gene mutations is recommended and tumor testing for microsatellite instability (MSI) or deficient mismatch repair (dMMR) can be considered. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-B).

[vv] SBRT to metastases can be considered in patients with oligometastatic progression where progression-free survival is the goal.

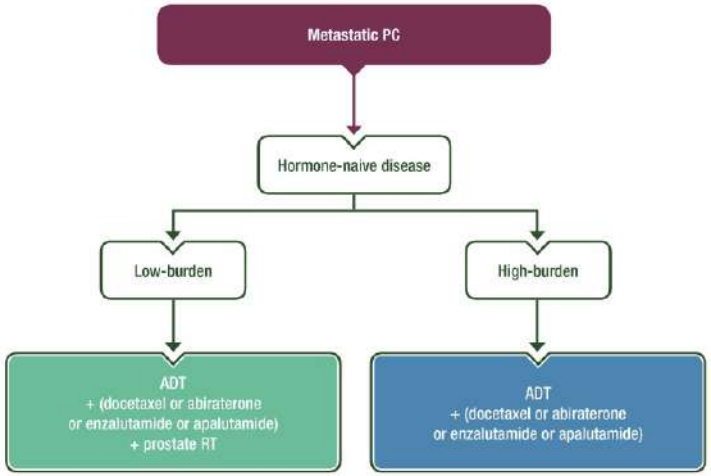
[ww] Routine use of bone antiresorptive therapy is not recommended in the castration-naïve setting unless for elevated fracture risk (see PROS-H).

[xx] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

[yy] See Principles of Non-Hormonal Systemic Therapy (PROS-I).

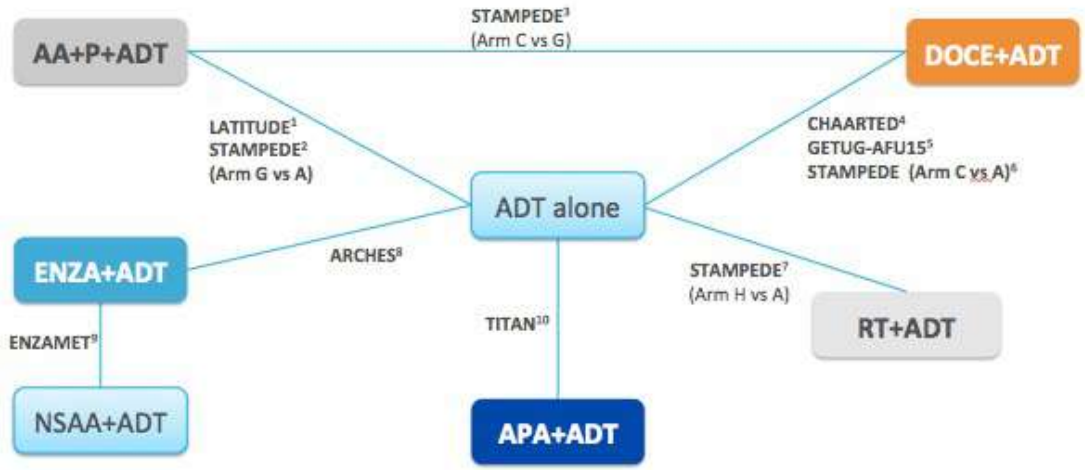
[zz] Patients who were under monitoring for M0 disease should receive an appropriate therapy for castration-naïve disease.

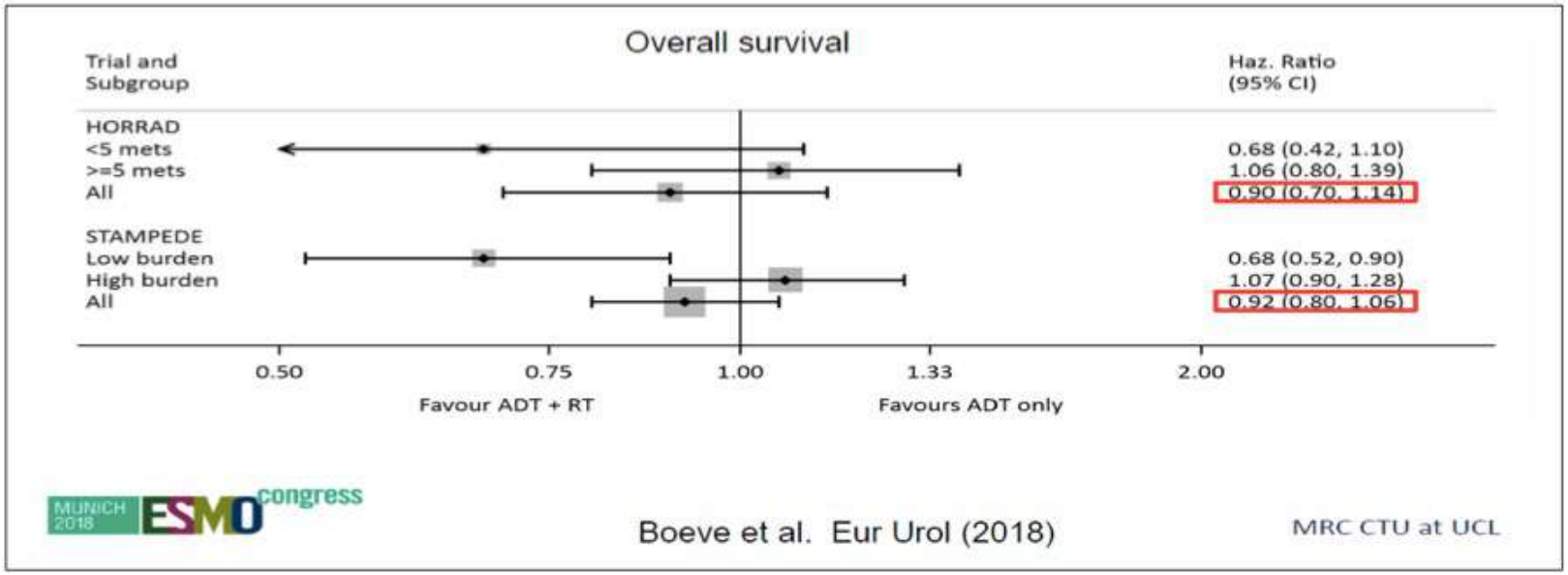
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit for the regimen.	Strong
Offer ADT combined with prostate radiotherapy (using the doses from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high-volume M1 disease (CHAARTED criteria) outside of clinical trials	Strong



STUDI FARMACOLOGICI

- TITAN: ADT vs ADT + Apalutamide
- ARCHES: ADT vs ADT + Enzalutamide
- ENZAMET: ADT + AA ± Docetaxel vs ADT + Enzalutamide ± Docetaxel
- LATITUDE: ADT vs ADT + Abiraterone
- STAMPEDE-G: ADT vs ADT + Abiraterone
- STAMPEDE-C: ADT vs ADT + Docetaxel
- CHAARTED: ADT vs ADT + Docetaxel
- GETUG-AFU15: ADT vs ADT + Docetaxel

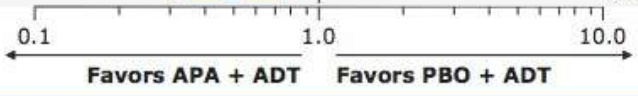




TITAN Final Analysis

Overall survival subgroup analysis

Subgroup	No. of events/no. of patients		Median overall survival (mo)		Hazard ratio for death (95% CI)
	APA + ADT	PBO + ADT	APA + ADT	PBO + ADT	
Disease volume					
High	134/325	175/335	NE	38.7	0.70 (0.56–0.88)
Low	36/200	60/192	NE	NE	0.52 (0.35–0.79)



STUDI IN CORSO 1

1	Not yet recruiting	Evaluation of dAroLutamide Addition to anDrogen Deprivation Therapy and radiatioN Therapy in Newly Diagnosed Prostate Cancer With Pelvic Lymph Nodes Metastases	• Prostate Cancer	• Drug: Darolutamide 300 mg • Drug: Placebo of Darolutamide
2	Not yet recruiting	Different Fractionation Schedules of Radiotherapy to the Primary Tumour in Metastatic Hormone Sensitive Prostate Cancer	• Prostate Cancer • Radiotherapy Side Effect • Metastatic Cancer	• Radiation: Moderate hypo-fractionation • Radiation: Ultra-hypo-fractionation
3	Not yet recruiting	5500/20 vs. SABR or Brachytherapy for PRimary OligoMetastatic Prostate Cancer Treatment (PROMPT)	• Oligometastatic Prostate Cancer	• Radiation: Hypofractionated external beam radiotherapy • Radiation: High dose rate brachytherapy • Radiation: Permanent seed implant • Radiation: Stereotactic body radiotherapy
4	Recruiting	Metastatic Prostate Cancer Men's Attitudes Towards Treatment of the Local Tumour and Metastasis Evaluative Research	• Prostate Cancer Metastatic • Radiotherapy Side Effect • Surgery • (and 4 more...)	• Other: Semi-Structured Interview Healthcare Professional • Other: Semi-Structured Interview Patients • Other: Think Aloud Interview Patients • Other: Discrete Choice Experiment (DCE) Patients
5	Recruiting	Study of Abiraterone Acetate, Atezolizumab, GnRH Analog and Radiation Therapy in Men With Newly Diagnosed Hormone-sensitive Prostate Cancer	• Metastatic Prostate Cancer	• Drug: Atezolizumab • Drug: Abiraterone • Drug: Prednisone • (and 2 more...)
6	Recruiting	National Danish Protocol. Surgery+ SBRT for M1 Prostate Cancer Patients	• Prostate Cancer Metastatic	• Procedure: RARP • Radiation: SBRT • Drug: ADT
7	Recruiting	Local Ablative Therapy For Hormone Sensitive Oligometastatic Prostate Cancer	• Prostate Cancer Metastatic	• Radiation: Ablative Radiation Therapy • Other: Standard of care
8	Recruiting	Additional Treatments to the Local Tumour for Metastatic Prostate Cancer: Assessment of Novel Treatment Algorithms	• Prostate Cancer • Metastatic Prostate Cancer	• Combination Product: Standard of Care • Procedure: Minimally Invasive Ablative Therapy (MIAT) • Procedure: Radical Therapy (Prostatectomy or Radiotherapy)
9	Recruiting	Standard Systemic Therapy With or Without Definitive Treatment in Treating Participants With Metastatic Prostate Cancer	• Castration Levels of Testosterone • Metastatic Prostatic Adenocarcinoma • Stage IV Prostate Cancer AJCC v8 • (and 2 more...)	• Drug: Abiraterone • Drug: Bicalutamide • Drug: Degarelix • (and 12 more...)

STUDI IN CORSO 2

10	☑	Recruiting	Cytoreductive Prostatectomy Versus Cytoreductive Prostate Irradiation as a Local Treatment Option for Metastatic Prostate Cancer: a Multicentric Feasibility Trial	• Prostate Cancer Metastatic	• Procedure: radical prostatectomy • Radiation: Whole pelvis radiotherapy
11	☑	Recruiting	Antiandrogen Therapy, Abiraterone Acetate, and Prednisone With or Without Neutron Radiation Therapy in Treating Patients With Prostate Cancer	• Castration-Sensitive Prostate Carcinoma • Metastatic Malignant Neoplasm in the Bone • Metastatic Prostate Carcinoma • (and 5 more...)	• Drug: Antiandrogen Therapy • Drug: Abiraterone Acetate • Drug: Prednisone • Radiation: Radiation Therapy
12	☑	Recruiting	Multi-arm Multi-modality Therapy for Very High Risk Localized and Low Volume Metastatic Prostatic Adenocarcinoma	• Prostate Cancer	• Drug: Apalutamide • Drug: Abiraterone Acetate • Drug: Prednisone • (and 3 more...)
13	☑	Withdrawn	Feasibility Trial in Men With Hormone Sensitive Oligometastatic Prostate Cancer	• Hormone Sensitive Oligometastatic Prostate Cancer	• Procedure: Radical prostatectomy • Radiation: HDR (19Gy) or SBRT (35-40Gy)
14	☑	Recruiting	Systemic and Tumor-Directed Therapy for Oligometastatic Prostate Cancer	• Newly Diagnosed Oligometastatic Prostate Cancer	• Procedure: radical prostatectomy • Radiation: stereotactic body radiotherapy • Drug: Leuprolide • (and 2 more...)
15	☑	Recruiting	Pembrolizumab +/- SD-101 in Hormone-Naïve Oligometastatic Prostate Cancer With RT and IADT	• Prostatic Neoplasms	• Drug: Pembrolizumab • Drug: SD-101 • Drug: Leuprolide acetate • (and 3 more...)
16	☑	Unknown †	Carbon Ion Radiotherapy in Treating Patients Undergoing Systemic Therapy for Oligo-metastatic Prostate Cancer	• Metastatic Prostate Carcinoma	• Radiation: CIRT with systemic therapy arm
17	☑	Unknown †	Hormone Therapy With or Without Definitive Radiotherapy in Metastatic Prostate Cancer	• Prostate Cancer	• Radiation: Radiotherapy to the pelvis • Drug: Hormonal therapy (LHRH agonist and/or antiandrogens)
18	☑	Active, not recruiting	Stereotactic Radiotherapy for Oligometastatic Prostate Cancer	• Prostatic Neoplasms	• Radiation: stereotactic radiotherapy
19	☑	Active, not recruiting	Radiotherapy for Oligometastatic Prostate Cancer	• Oligometastatic Prostate Cancer	• Radiation: Stereotactic radiation
20	☑	Unknown †	Best Systemic Therapy or Best Systemic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery)	• Prostate Cancer	• Other: Best Systemic Therapy (BST) • Other: Best Systemic Therapy (BST) + Surgery or Radiation Therapy • Behavioral: Questionnaires • Other: Phone Call/Email

ONCOLOGY IMAGING

Non-palliative radiotherapy in ab initio oligometastatic prostate cancer: an Italian national survey

Giorgia Timon[1] · Barbara Alicja Jereczek-Fossa[2,3] · Sergio Fersino[4] · Cinzia Iotti[1] · Renzo Corvò[5] · Stefano Maria Magrini[6] · Filippo Alongi[7,8]

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Table 2 Answers to question 9: "what imaging technique do you consider mandatory to evaluate this subset of patients?"

Answer	Respondents (%)
Choline- or PSMA-PET/CT	92
CT scan of the thorax and abdomen	35
Bone scan	26
MRI of the abdomen/pelvis/prostate, including mpMRI	38
Whole-body MRI	9

Table 3 Answers to question 11: "what volumes would you treat?"

Answer	Respondents (%)
Prostate AND up to 4–5 secondary lesions	20
Prostate AND up to 2–3 secondary lesions	69
Up to 4–5 secondary lesions only	3
Up to 2–3 secondary lesions only	7
Prostate only	0
No radiation	1

PITFALLS

- Low-volume vs oligometastatico
- Stadiazione
- Traslazione di dati → letteratura vs real life
- Fenomeno di Will-Rogers/stage migration
- Dati di combinazione: PEACE-1, ATLAS, ENZARAD
- Popolazione eterogenea, assenza biomarkers
- Dosi, volumi, tecnica

Summary of evidence	LE
PSMA PET/CT is more accurate for staging than CT and bone scan but to date no outcome data exist to inform subsequent management.	1b

	High	Low
CHAARTED (volume)	≥ 4 Bone metastasis including ≥ 1 outside vertebral column or pelvis **OR** Visceral metastasis	Not high
LATITUDE (risk)	≥ 2 high-risk features of: • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high

OMD. Future prospective studies should consider stratifying patients into different categories, e.g., such as will be performed in the context of the OligoCare trial. Meanwhile, based on the available evidence, indications for curative intent radiotherapy of OMD can be defined as 1 to 5 metastatic lesions, with a controlled primary tumor being optional, but where all metastatic sites must be safely treatable.

between conventional fractionation and ultra-HFX [659]. Therefore, it seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Lievens Y, Radiother Oncol. 2020; EAU guidelines

CONCLUSIONI

- ✓ A CHI → de novo mCSPC low volume/oligomet (mCSPC high volume in RP/RC; mCRPC in PD solo su T)
- ✓ COME → dosi "radicali" ipofrazionate, volumi, IMRT+IGRT?, T+M?, + ARTA
- ✓ QUANDO → ASAP dopo avvio ADT
- ✓ PERCHÉ → perché no?

…Verso un approccio combinato e precoce

MDT!

Grazie!