Treatment intensification with radiotherapy: does volume matter?

Nicholas James

@Prof_Nick_James

ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

Metastatic prostate cancer

- 20 years ago, treatment was very simple
  - Locally advanced or metastatic disease → long term androgen deprivation, on relapse, refer for palliative care

Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol

Gerhardt Attard, Louise Brown, Noel Clarke, Laura Murphy, William Cross, Rob Jones, Silke Gillessen, J.Martin Russell, Adrian Cook, Jo Bowen, Anna Lydon, Ian Pedley, Omi Parikh, Simon Chowdhury, Zafar Malik, David Matheson, Chris Parker, Matthew Sydes, Mahesh Parmar, Nicholas James **on behalf of the STAMPEDE investigators***

Conducted by Medical Research Council Trials Unit at University College London, U.K.

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544

*113 U.K. and Swiss sites: list of investigators and collaborators at www.stampedetrial.org

2021 ESMO congress

STAMPEDE

- Recruits men from 4 groups starting long-term ADT:
  1. **High-risk localised (T3/4, PSA >40 or Gleason 8-10)**
  2. **Node-positive (N+) prostate cancer**
  3. Newly-diagnosed metastatic (M1)
  4. high-risk recurrence post surgery or RT

- Radical radiotherapy in standard care:
  - N+M0 patients; optional
  - N0M0 patients; optional Oct 2005 – Nov 2011, mandatory from Nov-2011

www.stampedetrial.org

STAMPEDE

- Recruits men from 4 groups starting long-term ADT:

Around 40% micro-M1 on PSMA PET or wbMRI

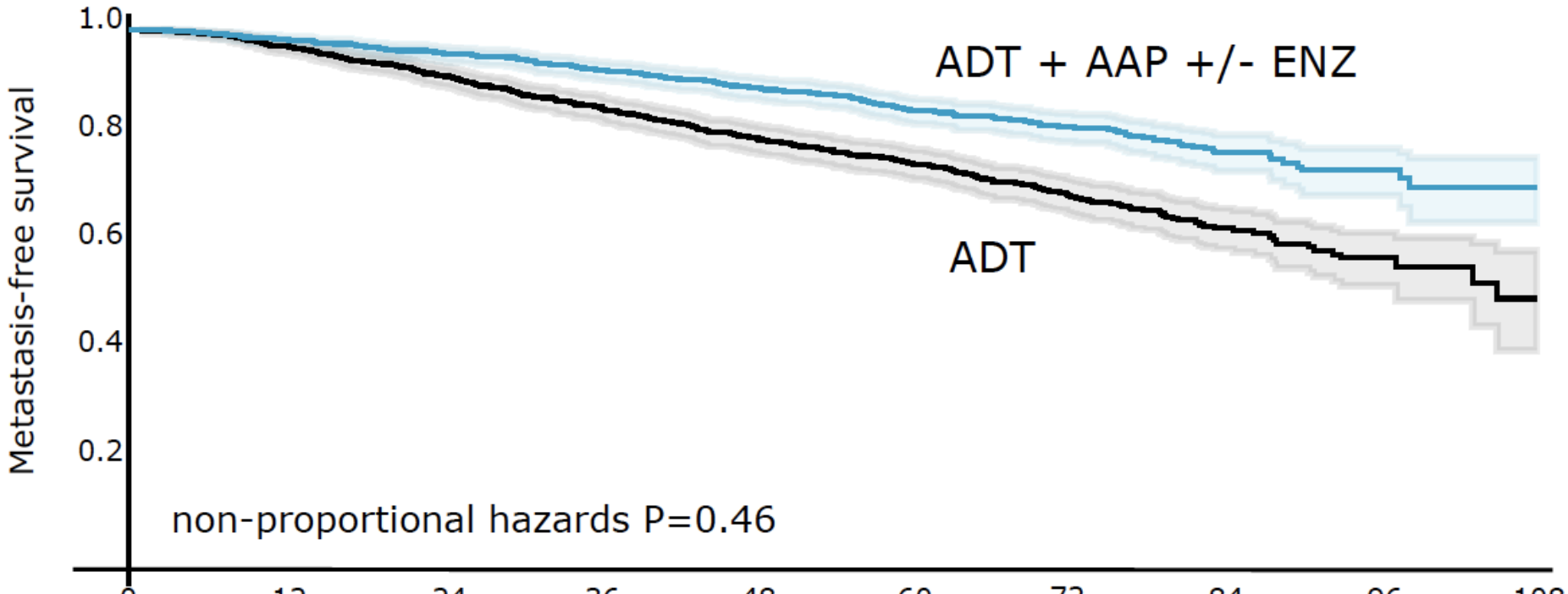
2. Node positive (N+) prostate cancer
3. Newly-diagnosed metastatic (M1)
4. high-risk recurrence post surgery or RT

- Radical radiotherapy in standard care:
  - N+M0 patients; optional
  - N0M0 patients; optional Oct 2005 – Nov 2011, mandatory from Nov-2011

www.stampedetrial.org

STAMPEDE

Primary endpoint: metastasis-free survival



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Events
180 ADT+ AAP +/- ENZ
306 ADT

HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

6-year MFS improved from 69% to 82%

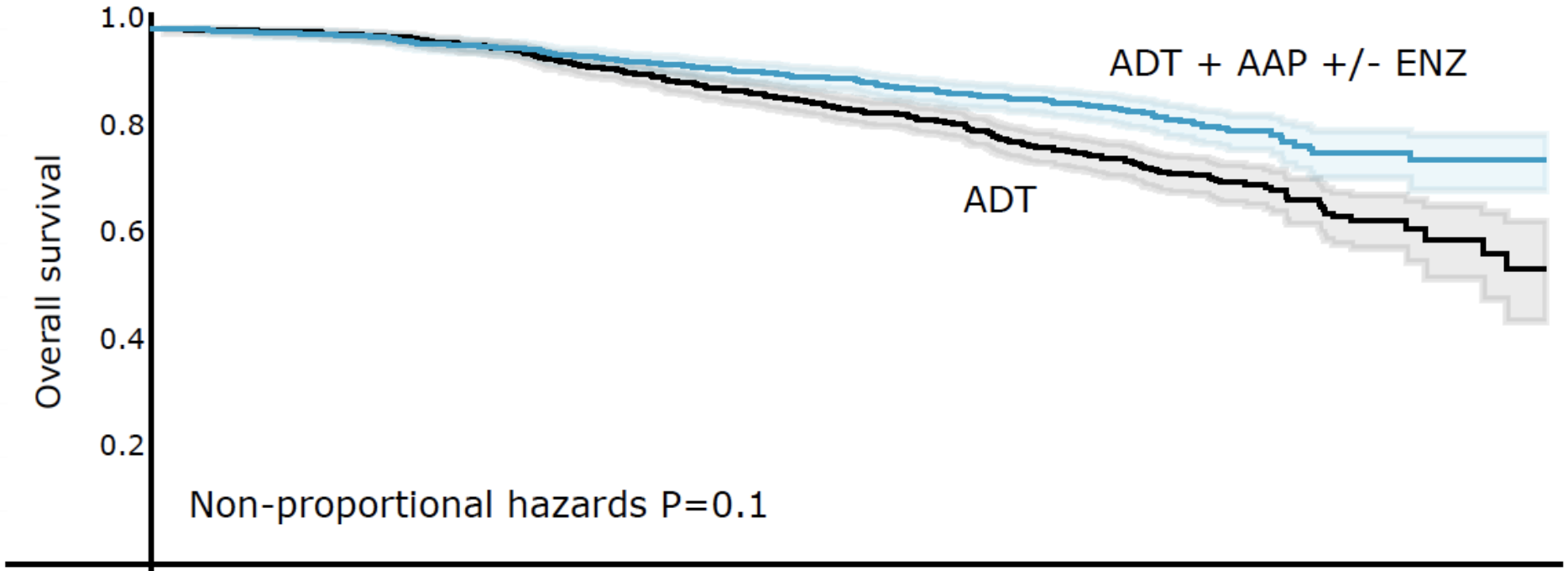
Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards P=0.46

2021 ESMO congress

Overall survival

Events
147 ADT+AAP +/- ENZ
236 ADT



SOC										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
SOC+AAP+/-ENZ										
At-risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

HR: 0.60
95% CI 0.48 to 0.73
P value 9.3×10^{-7}

6-year survival improved from 77% to 86%

Kaplan-Meier estimates with 95% CI in lighter shade

Volume effects – hormone sensitive prostate cancer [1–5]

Therapy	HV vs. LV Prognostic FFS	HV vs. LV Predictive FFS	HV vs. LV Prognostic OS	HV vs. LV Predictive OS
Docetaxel	Yes	Only in metachronous disease	Yes	Only in metachronous disease
Abiraterone	Yes	No	Yes	No
Enzalutamide	Yes	No	Yes	No
Apalutamide	Yes	No	Yes	No
Radiotherapy	Yes	Yes	No	Yes

HV, high volume; FFS, failure-free survival; LV, low volume; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival.

1. Clarke NW, et al. Ann Oncol. 2019;30(12):1992–2003; 2. Fizazi K, et al. Lancet Oncol. 2019;20(5):686–700; 3. Davis ID, et al. N Engl J Med. 2019;381(2):121–131; 4. Chi KN, et al. N Engl J Med. 2019;381(1):13–24; 5. Parker CC, et al. Lancet. 2018;392(10162):2353–2366.

Volume effects – hormone sensitive prostate cancer [1–5]

Therapy	HV vs. LV Prognostic FFS	HV vs. LV Predictive FFS	HV vs. LV Prognostic OS	HV vs. LV Predictive OS
Docetaxel	Yes	Only in metachronous disease	Yes	Only in metachronous disease
Abiraterone	Yes	No	Yes	No
Enzalutamide	Yes	No	Yes	No
Apalutamide	Yes	No	Yes	No
Radiotherapy	Yes	Yes	No	Yes

HV, high volume; FFS, failure-free survival; LV, low volume; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival.

1. Clarke NW, et al. Ann Oncol. 2019;30(12):1992–2003; 2. Fizazi K, et al. Lancet Oncol. 2019;20(5):686–700; 3. Davis ID, et al. N Engl J Med. 2019;381(2):121–131; 4. Chi KN, et al. N Engl J Med. 2019;381(1):13–24; 5. Parker CC, et al. Lancet. 2018;392(10162):2353–2366.

MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

STAMPEDE

UCL

Radiotherapy to the primary tumour for men with newly-diagnosed metastatic prostate cancer: Survival results from STAMPEDE

CC Parker, ND James, CD Brawley, NW Clarke, G Attard, S Chowdhury, W Cross, DP Dearnaley, S Gillessen, C Gilson, RJ Jones, MD Mason, R Millman, C Eswar, J Gale, JF Lester, DJ Sheehan, AT Tran, MKB Parmar, MR Sydes.

MUNICH 2018 ESMO congress

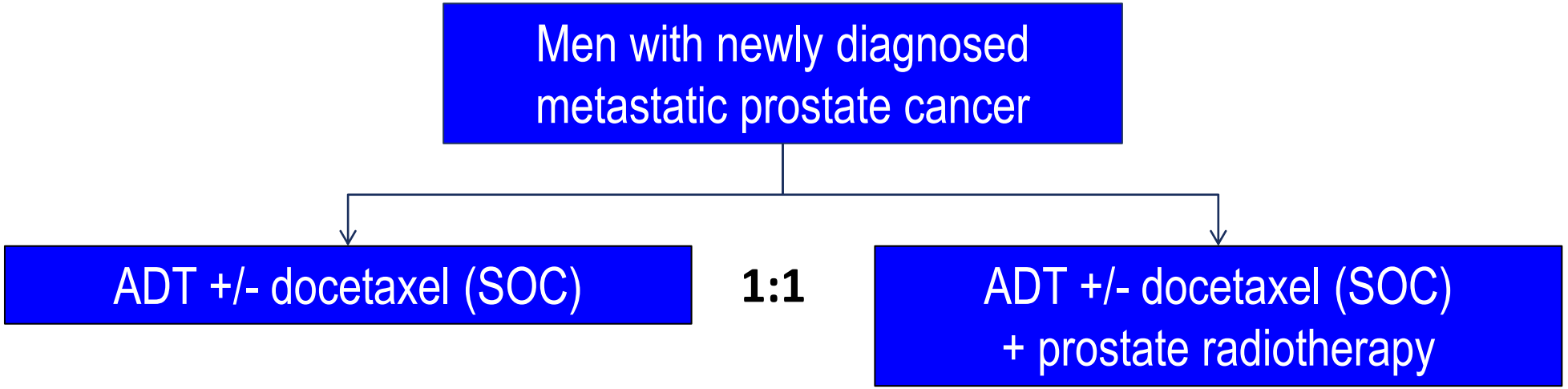
The ROYAL MARSDEN NHS Foundation Trust

CANCER RESEARCH UK

Background

- Men with metastatic prostate cancer receive systemic treatment
- We hypothesised that treatment to the primary tumour would improve overall survival in men with metastatic prostate cancer
- …and that the survival benefit would be greater in men with a lower metastatic burden

Study design



36Gy/6 fractions/6 weeks **or** 55Gy/20 fractions/4 weeks
Schedule nominated before randomisation

Stratification variables

Age (<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site,
WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use

Outcome measures

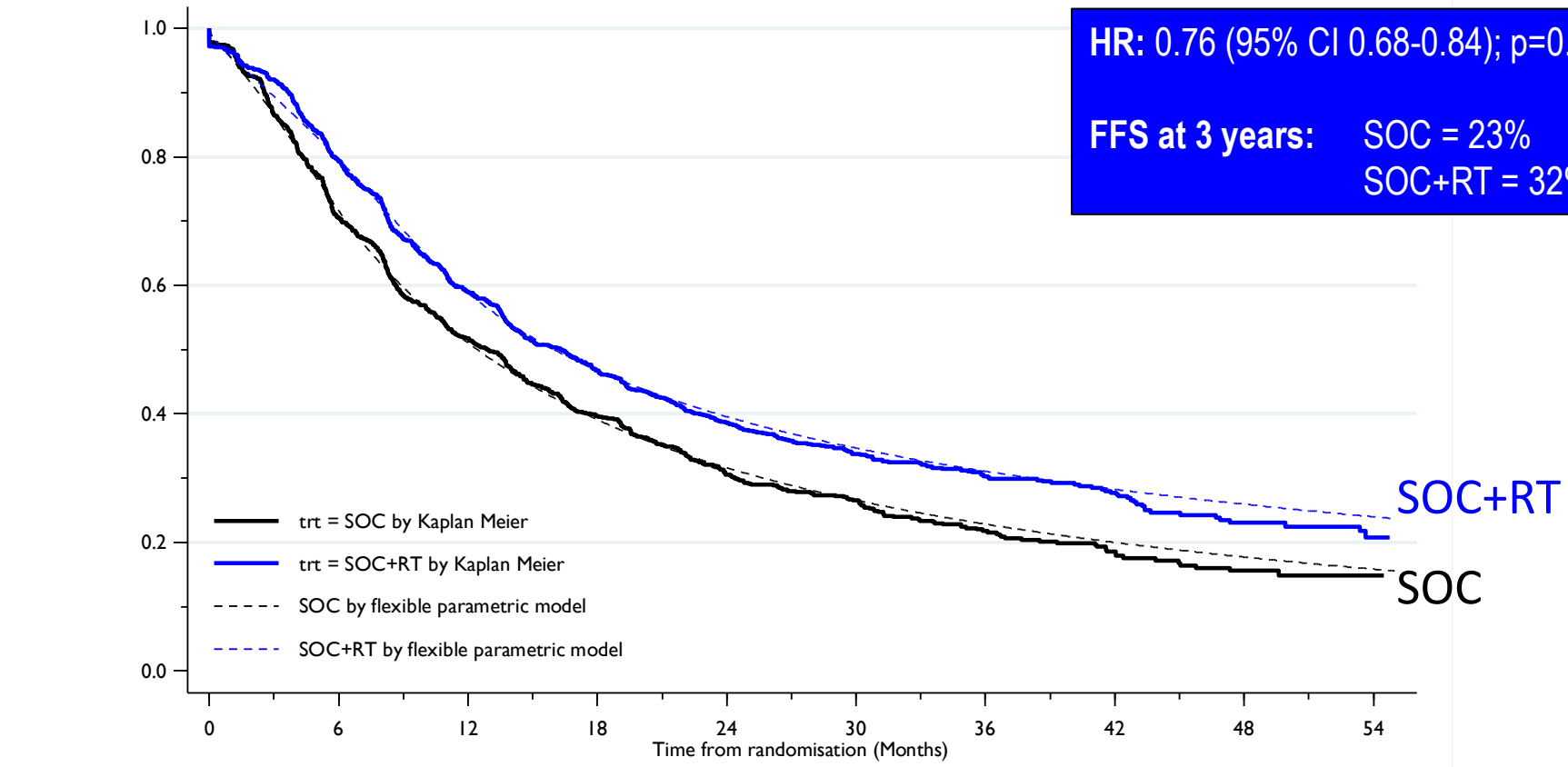
- Main outcome measure: **Overall survival**
- Secondary outcome measures:
  - **Failure-free survival**
  - **Symptomatic local events (SLE)**
  - **Toxicity**
  - Progression-free survival
  - Metastatic progression-free survival
  - Cause specific survival
  - Symptomatic skeletal events
  - Quality of life

RESULTS: Baseline characteristics

Characteristic		SOC (n=1029)	SOC+RT (n=1032)
Age (years)	Median (IQR) Range	68 (63-73) 37-86	68 (63-73) 45-87
PSA (ng/ml)	Median (IQR) Range	98 (30-316) 1-20590	97 (33-313) 1-11156
Metastatic burden	Low High Not classified	409 (42%) 567 (58%) 53	410 (43%) 553 (57%) 69
Site of metastases	Bone Liver Lung Distant lymph nodes Other	919 (89%) 23 (2%) 42 (4%) 294 (29%) 35 (3%)	917 (89%) 19 (2%) 48 (5%) 304 (29%) 33 (3%)
Docetaxel use	No Yes	845 (82%) 184 (18%)	849 (82%) 183 (18%)

Failure-free survival: all patients

Events 758 SOC | 685 SOC+RT

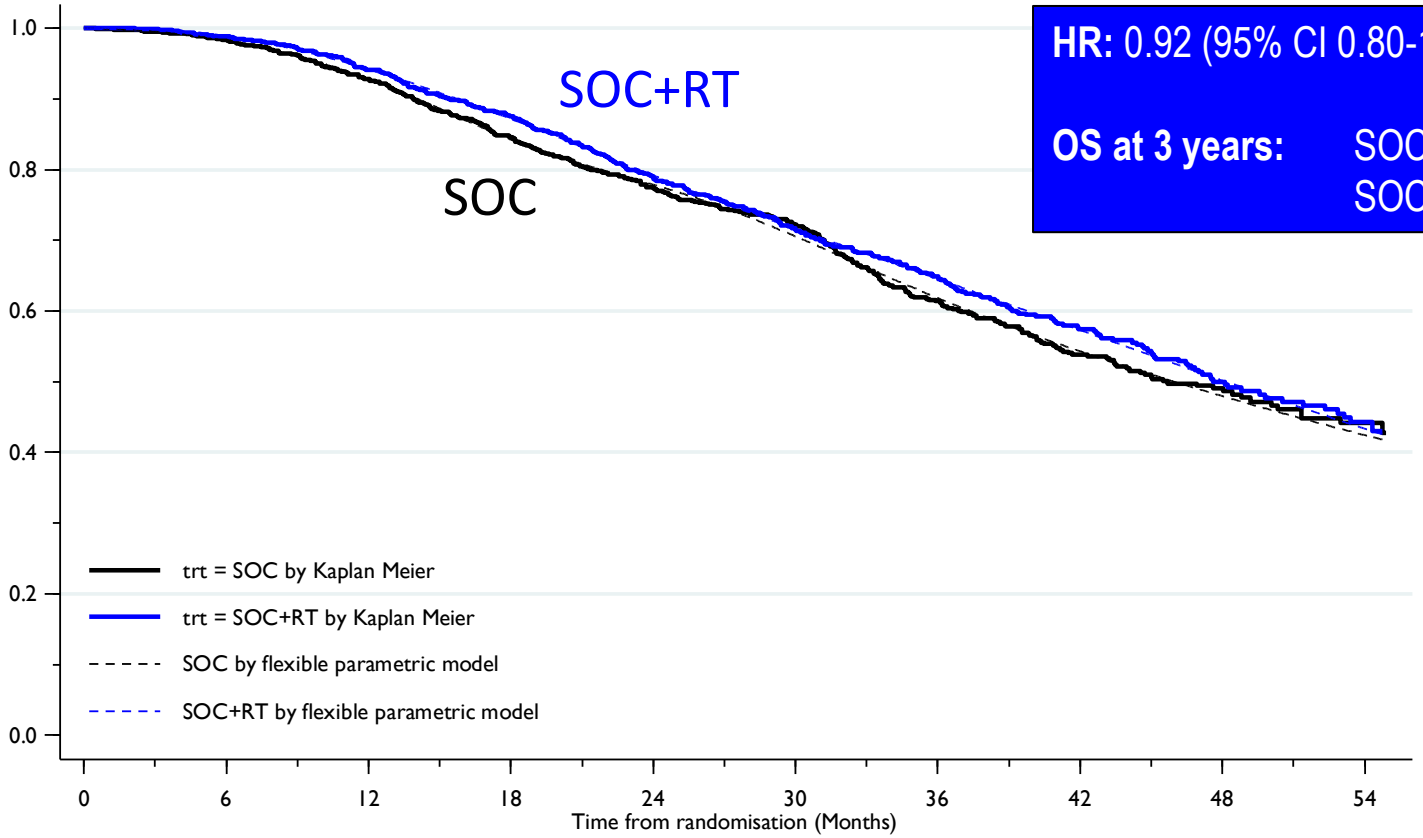


Number of patients (events)

SOC	1029	(300)	711	(189)	516	(119)	380	(76)	216	(26)	149	(25)	99	(13)	58	(8)	31	(1)	11
SOC+RT	1032	(211)	799	(203)	588	(120)	440	(70)	285	(33)	212	(20)	156	(11)	101	(14)	48	(3)	18

Overall survival: all patients

Events 391 SOC | 370 SOC+RT



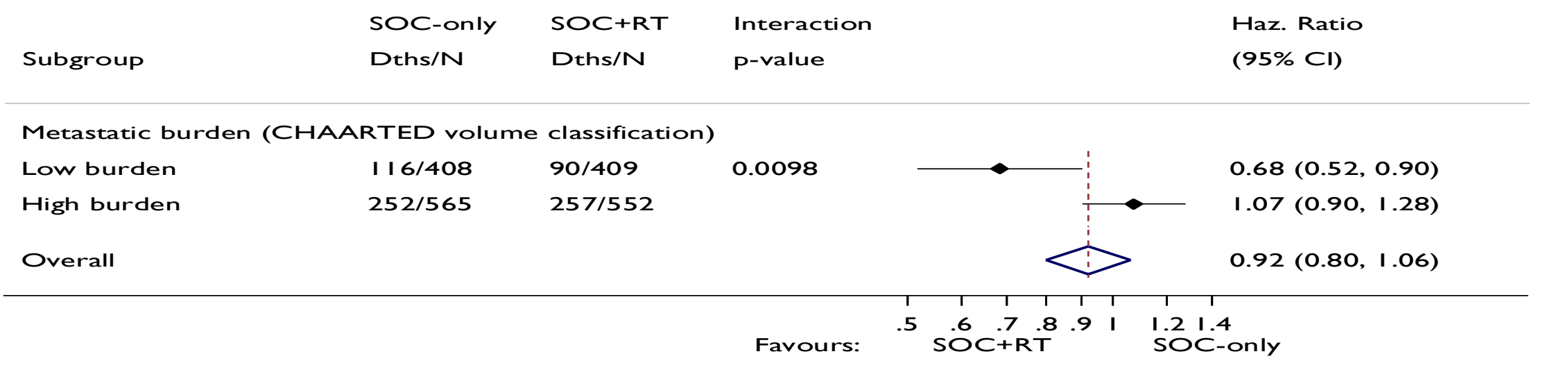
HR: 0.92 (95% CI 0.80-1.06); p=0.266

OS at 3 years: SOC = 62%
SOC+RT = 65%

Number of patients (events)

SOC	1029	(17)	998	(56)	933	(82)	826	(63)	601	(39)	481	(67)	328	(37)	219	(16)	122	(9)	41
SOC+RT	1032	(12)	998	(47)	936	(64)	832	(75)	611	(54)	478	(41)	365	(37)	236	(25)	128	(11)	47

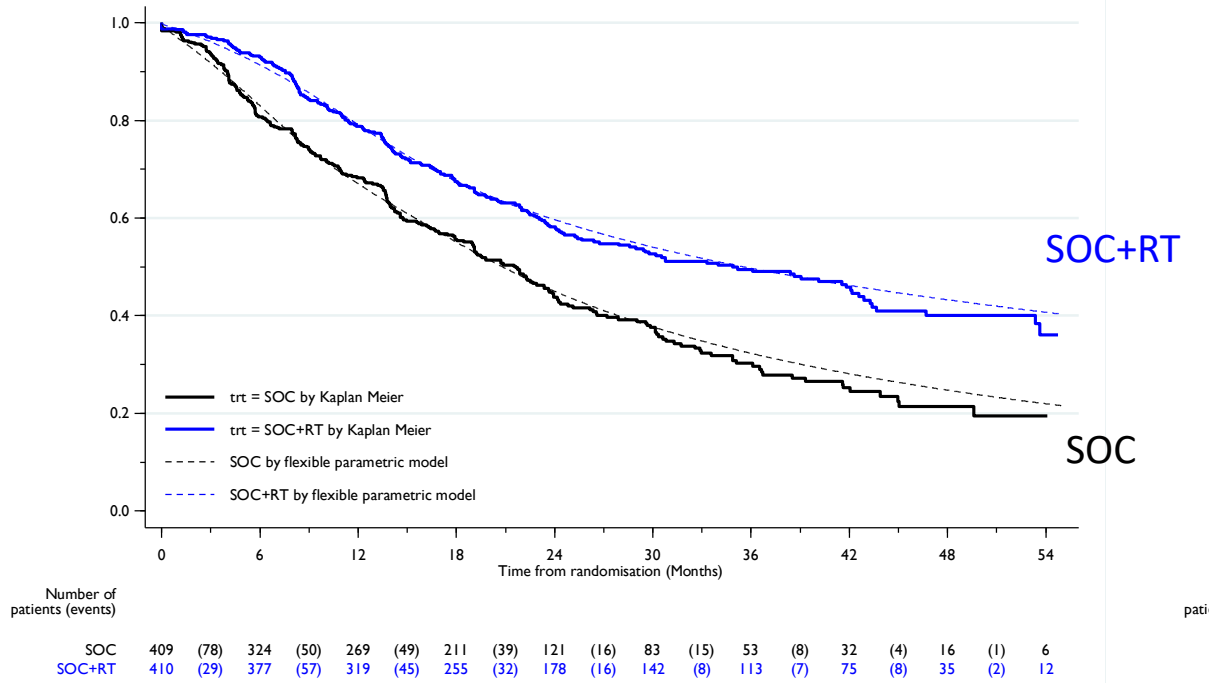
Overall survival: subgroup analysis by metastatic disease burden



Clear evidence that effect size does differ by disease burden (p=0.0098)

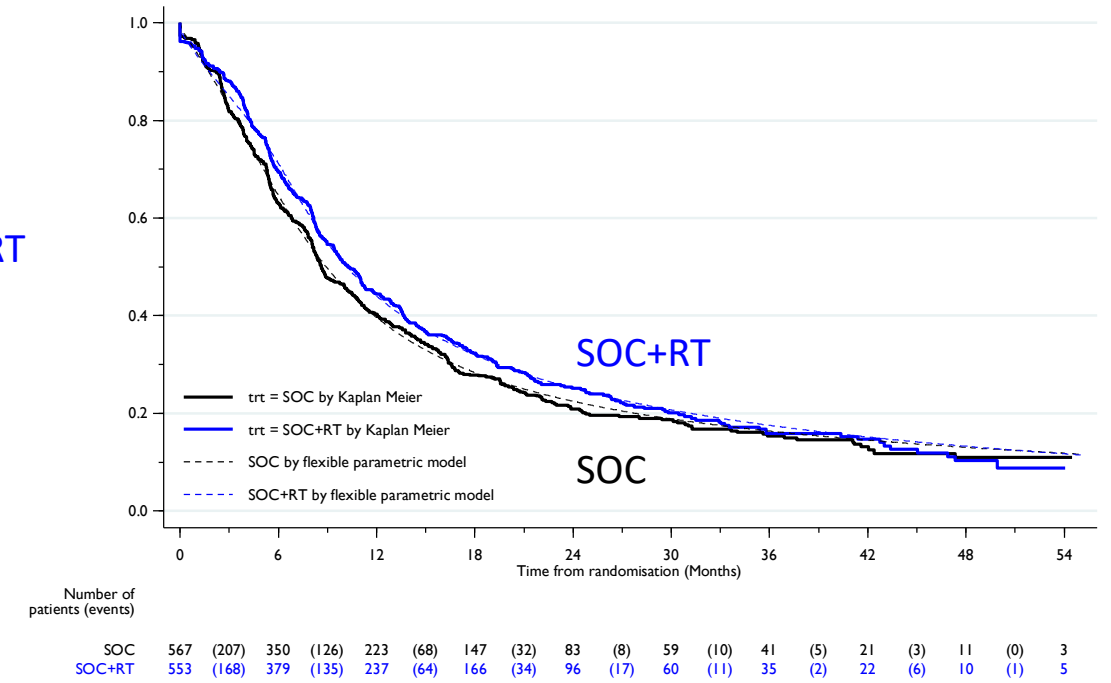
STAMPEDE Failure-free survival: metastatic burden subgroup analysis

Low burden



HR: 0.59 (95% CI 0.49-0.72); $p=4.83 \times 10^{-8}$
3 year FFS: SOC = 33%
SOC+RT = 50%

High burden

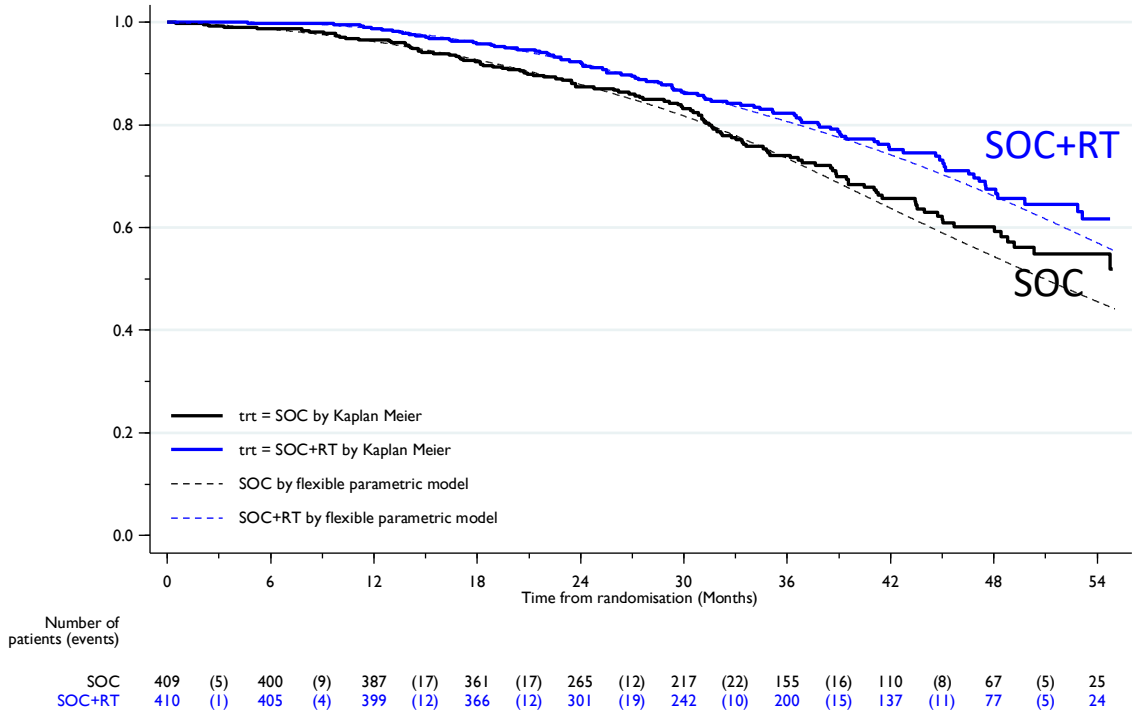


HR: 0.88 (95% CI 0.77-1.01); p=0.059
3 year FFS: SOC = 17%
SOC+RT = 18%

Test for interaction: p = 0.0024

DISCUSSION: Overall survival: metastatic burden subgroup analysis

Low burden

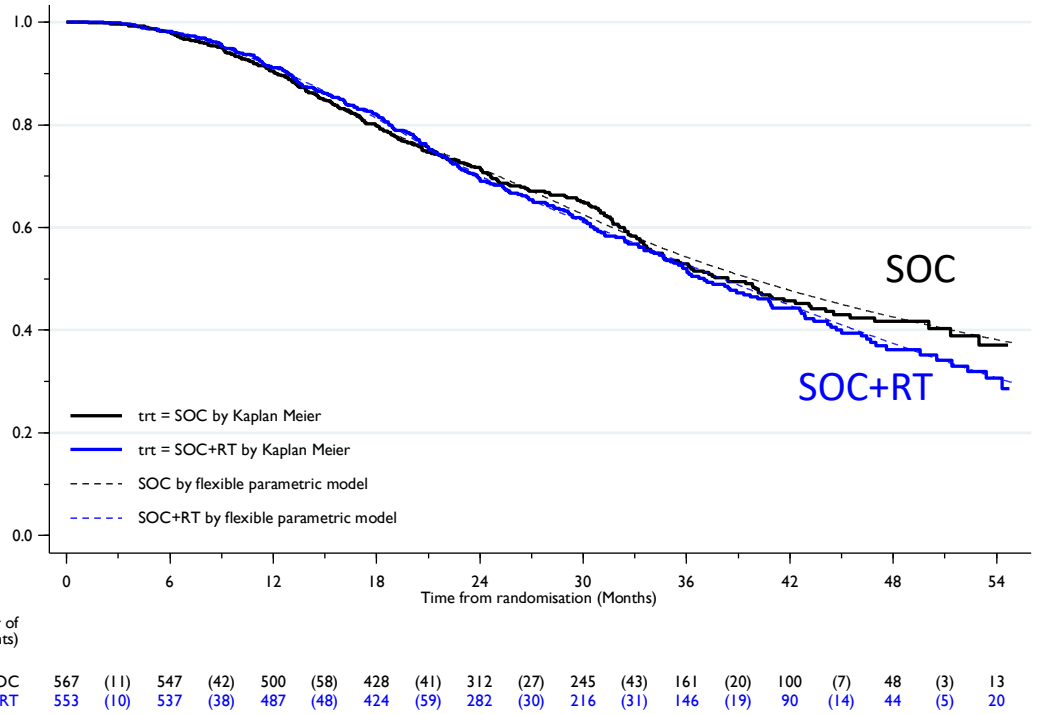


Number of patients (events)

SOC	409	(5)	400	(9)	387	(17)	361	(17)	265	(12)	217	(22)	155	(16)	110	(8)	67	(5)	25
SOC+RT	410	(1)	405	(4)	399	(12)	366	(12)	301	(19)	242	(10)	200	(15)	137	(11)	77	(5)	24

HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

High burden

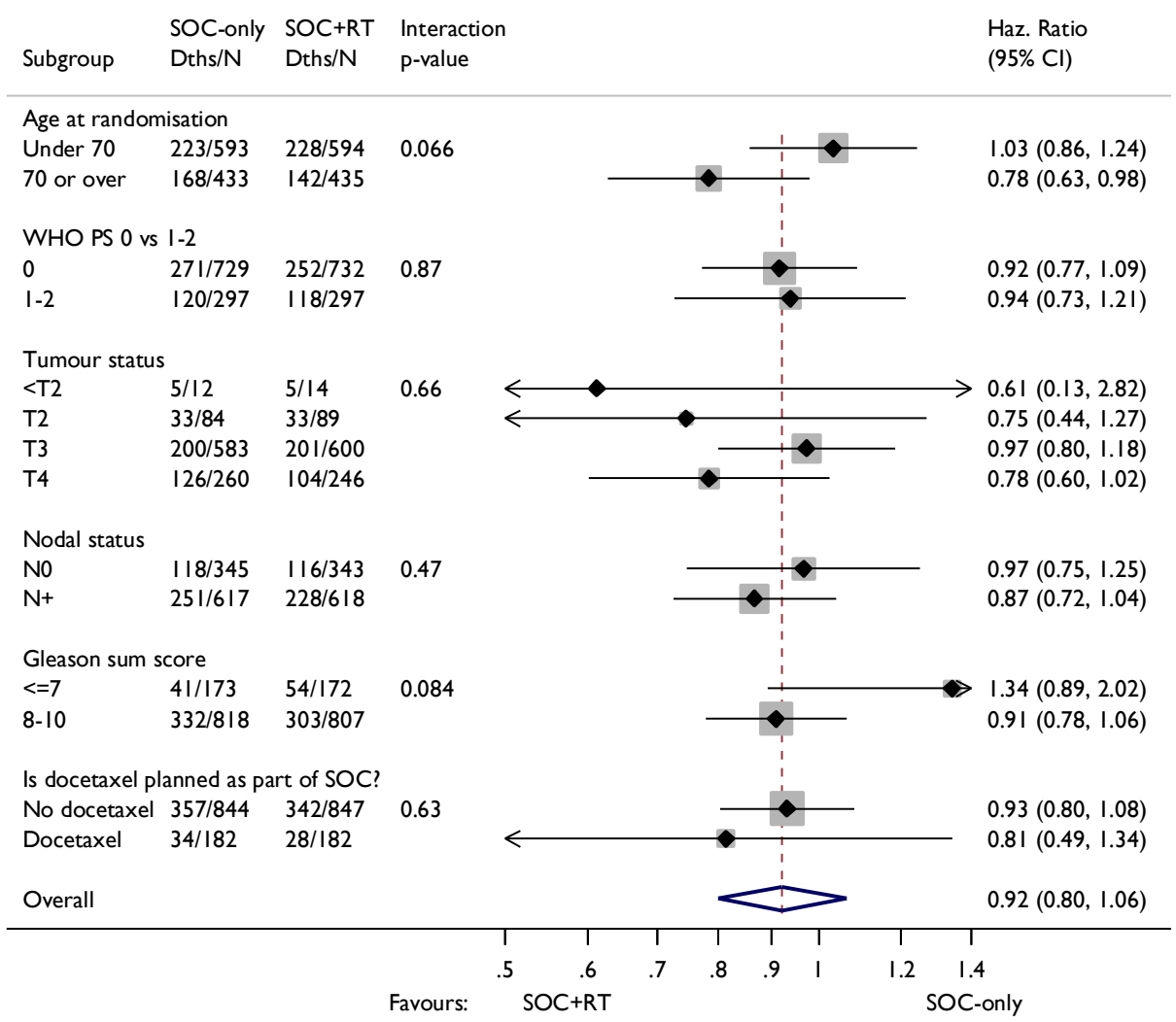


Number of patients (events)

SOC	567	(11)	547	(42)	500	(58)	428	(41)	312	(27)	245	(43)	161	(20)	100	(7)	48	(3)	13
SOC+RT	553	(10)	537	(38)	487	(48)	424	(59)	282	(30)	216	(31)	146	(19)	90	(14)	44	(5)	20

HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

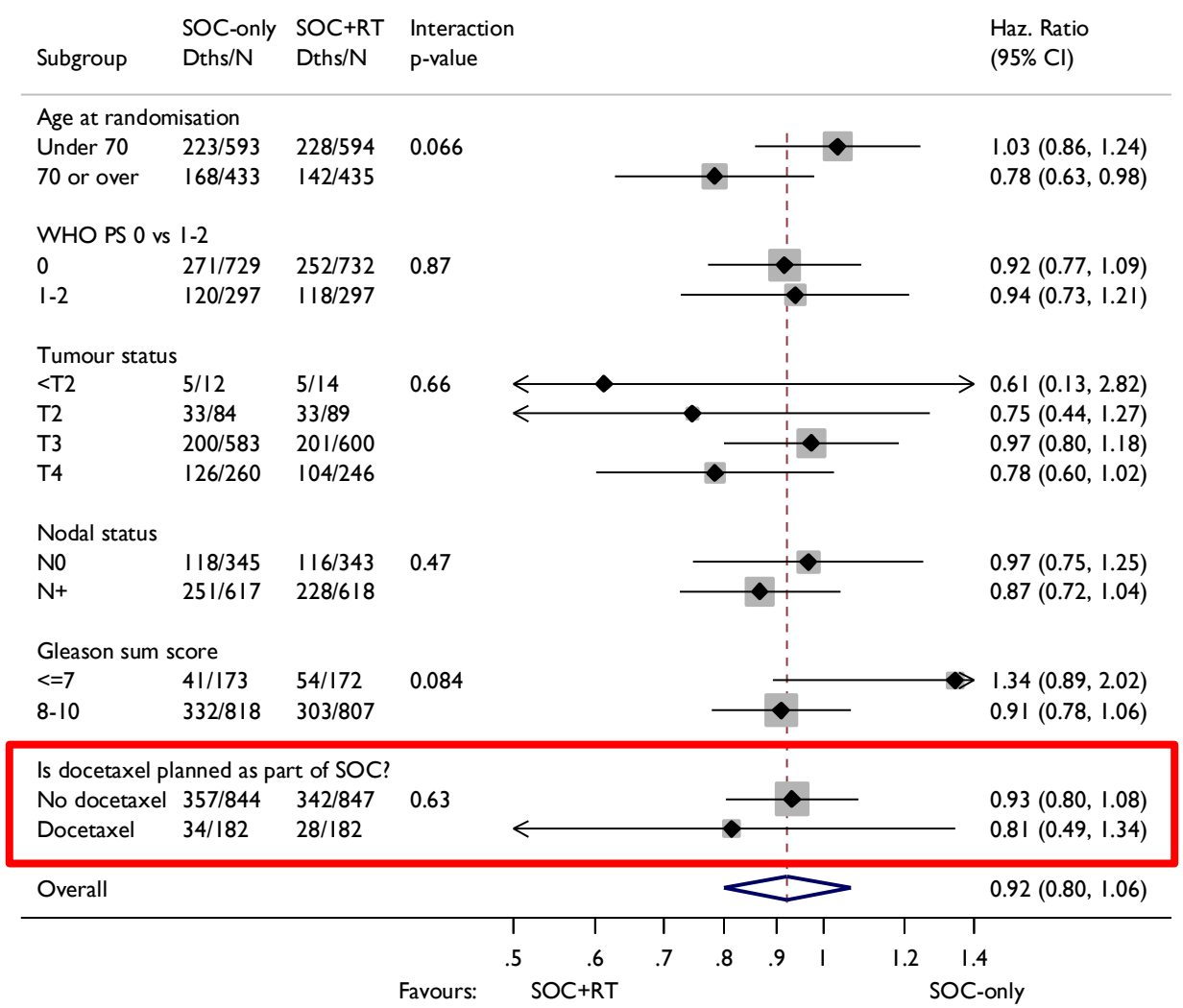
Overall survival: exploratory consistency analyses by baseline features



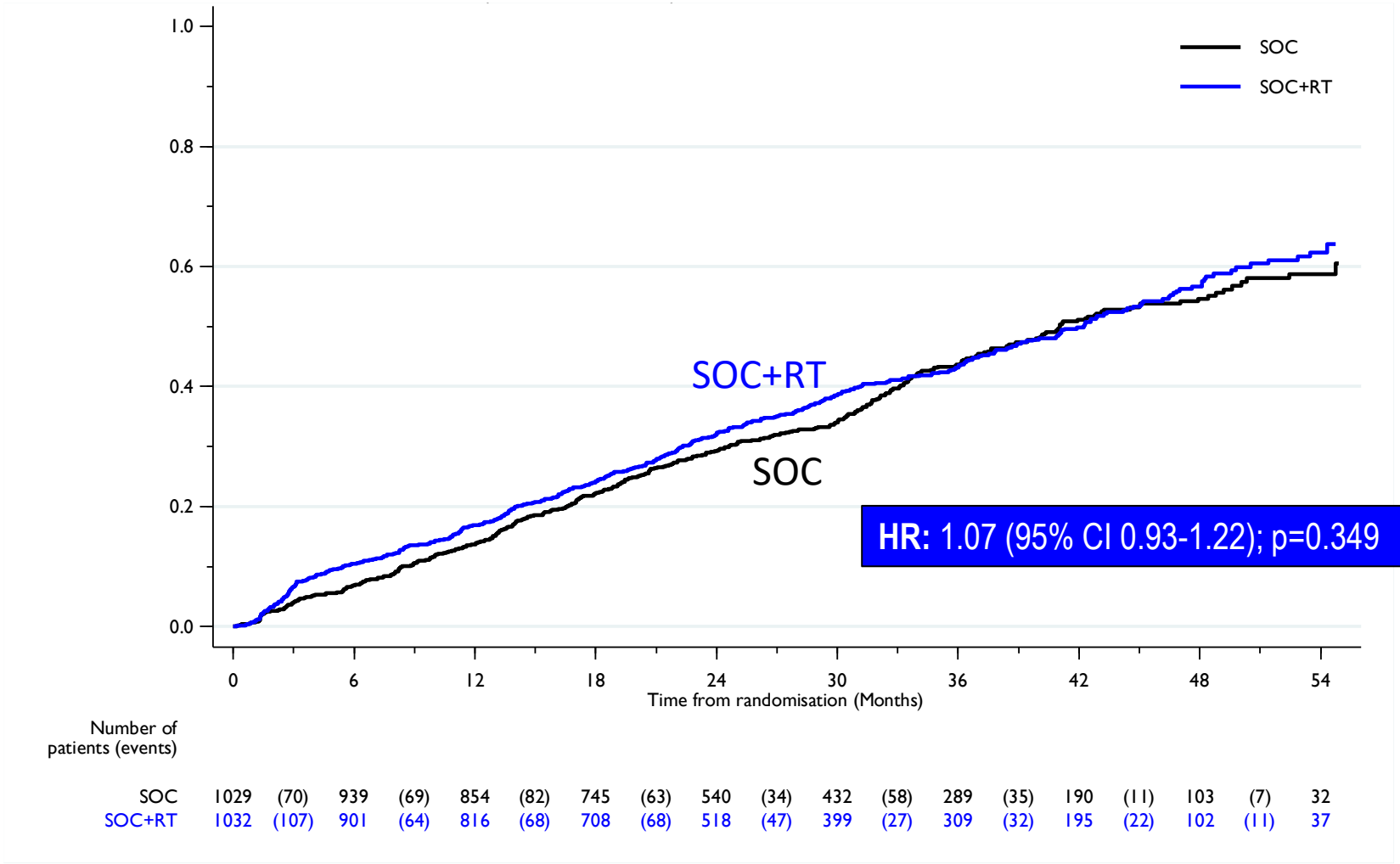
MUNICH 2018 ESMO congress

MRC CTU at UCL

Overall survival: exploratory consistency analyses by baseline features



Time from randomisation to first symptomatic local event (SLE)



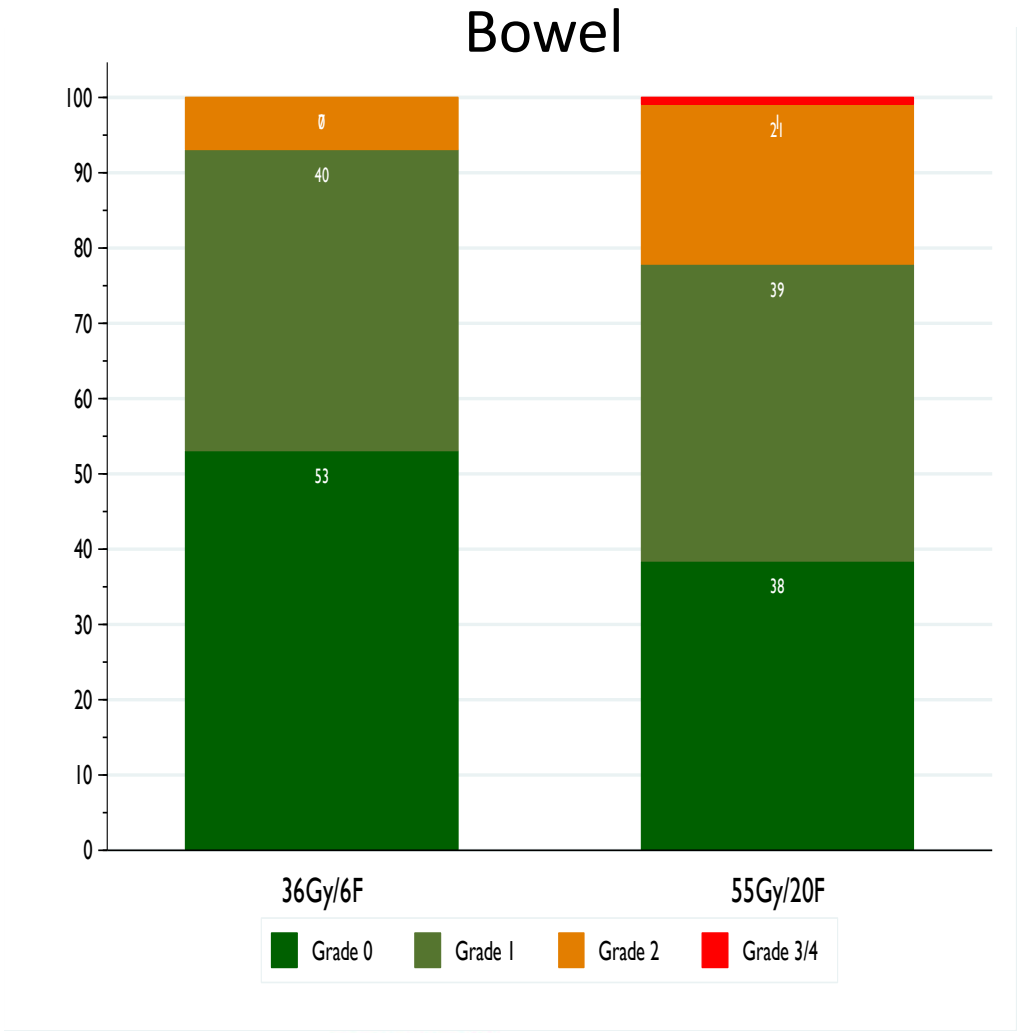
Number of patients (events)

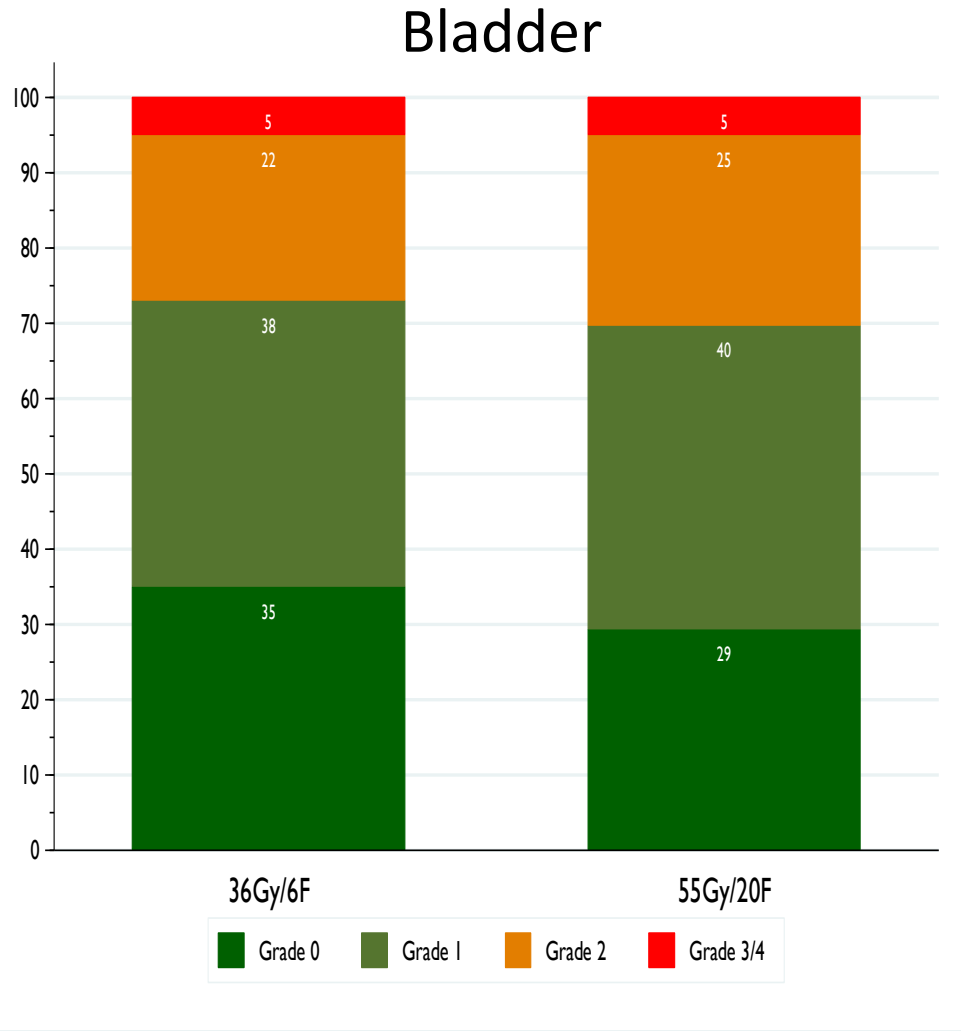
SOC	1029	(70)	939	(69)	854	(82)	745	(63)	540	(34)	432	(58)	289	(35)	190	(11)	103	(7)	32
SOC+RT	1032	(107)	901	(64)	816	(68)	708	(68)	518	(47)	399	(27)	309	(32)	195	(22)	102	(11)	37

Number of patients ever reporting each type of SLE

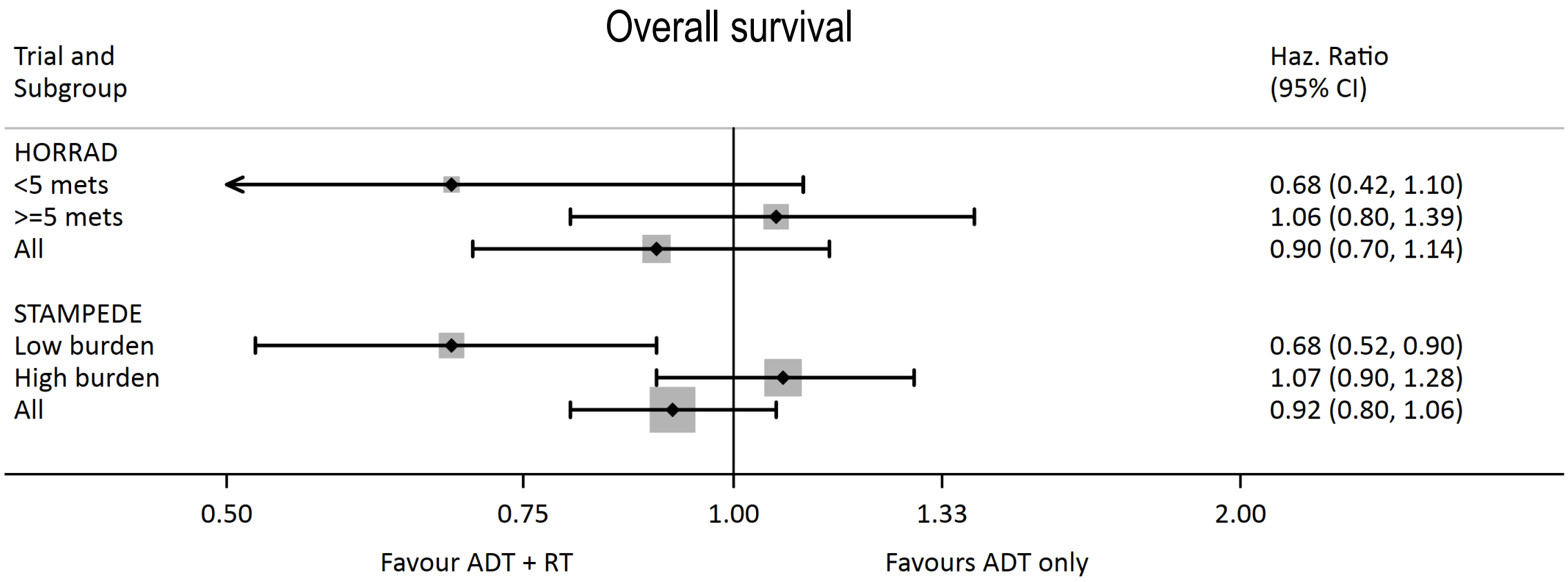
SLE type	SOC		SOC+RT	
	N	%	N	%
Urinary tract infection	62	6%	94	9%
Urinary catheter	46	4%	51	5%
TURP	32	3%	37	4%
Acute kidney injury	33	3%	38	4%
Urinary tract obstruction	25	2%	23	2%
Ureteric stent	18	2%	10	1%
Nephrostomy	10	1%	5	<1%
Colostomy	2	<1%	1	<1%
Surgery for bowel obs	0	0%	1	<1%
Total	**1029**	**100%**	**1032**	**100%**

Worst reported acute toxicity (RTOG scale) – by radiotherapy schedule





The effect is consistent with HORRAD



MUNICH 2018 ESMO congress

Boeve et al. Eur Urol (2018)

MRC CTU at UCL

Summary

- Prostate radiotherapy did not improve survival for unselected patients (HR=0·92, 95%CI 0·80-1·06; p=0.266)

- Prostate radiotherapy did improve survival (from 73% to 81% at 3 years) in those with a low metastatic burden (HR=0·68, 95%CI 0·52-0·90; p=0·007). Test for interaction: p=0.0098

- Prostate radiotherapy was well tolerated

Not all CHAARTED low volume is the same

The Team

Prof Noel Clarke

Alex Hoyle

Bone metastatic burden

Adnan Ali

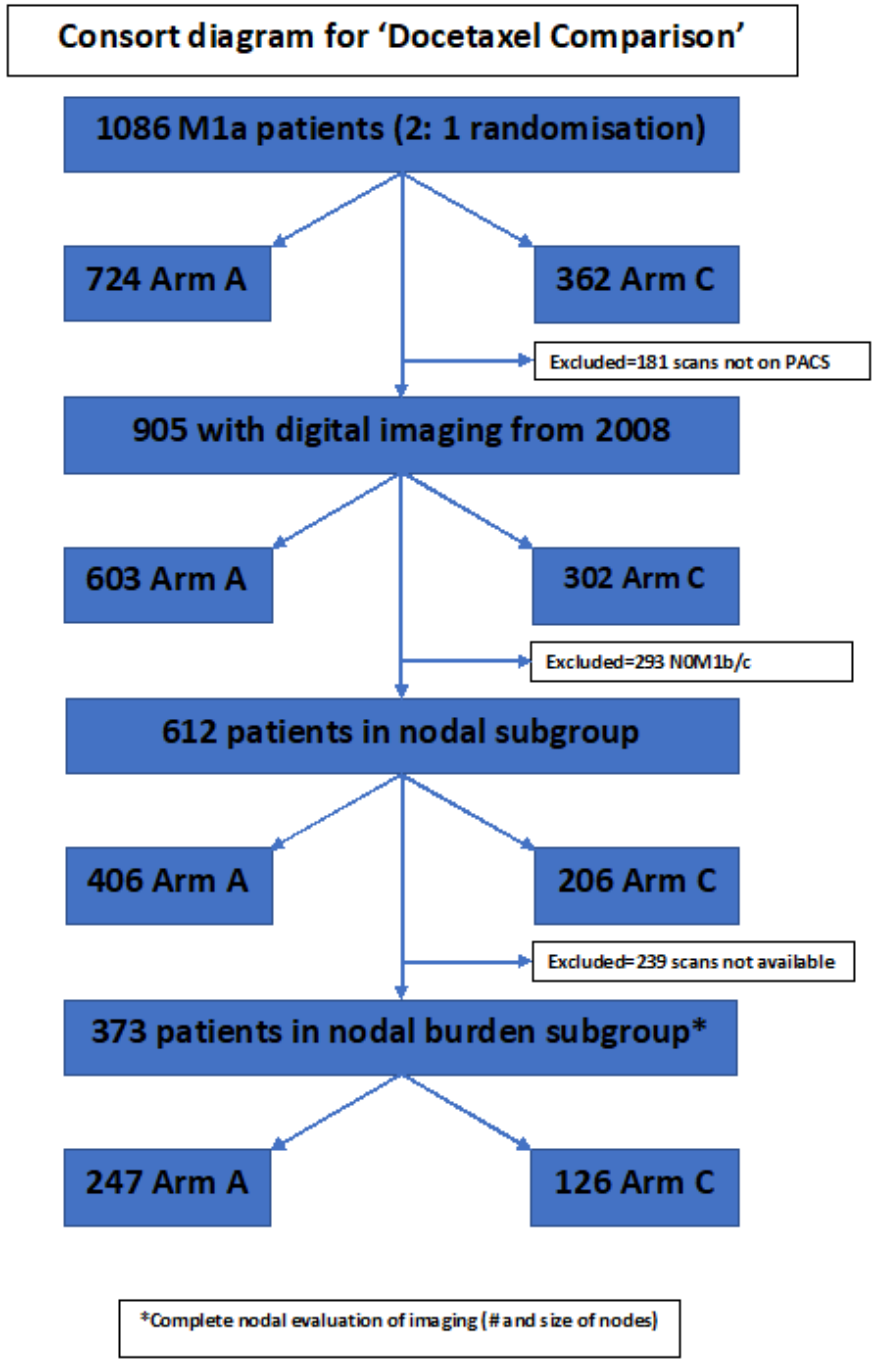
Áine Haran

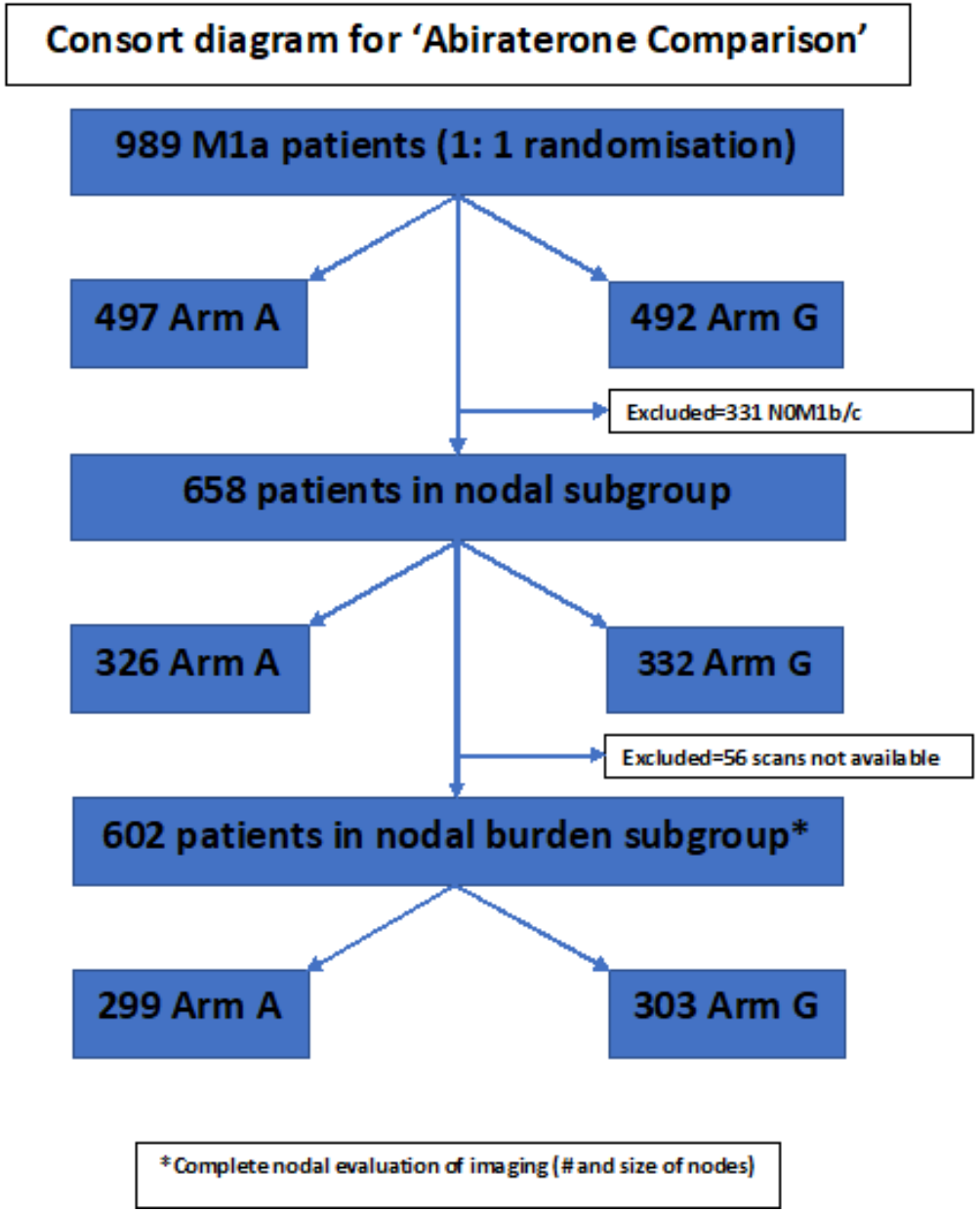
LN metastatic burden

Craig Jones

Toxicity assessment

Ashwin Sachdeva

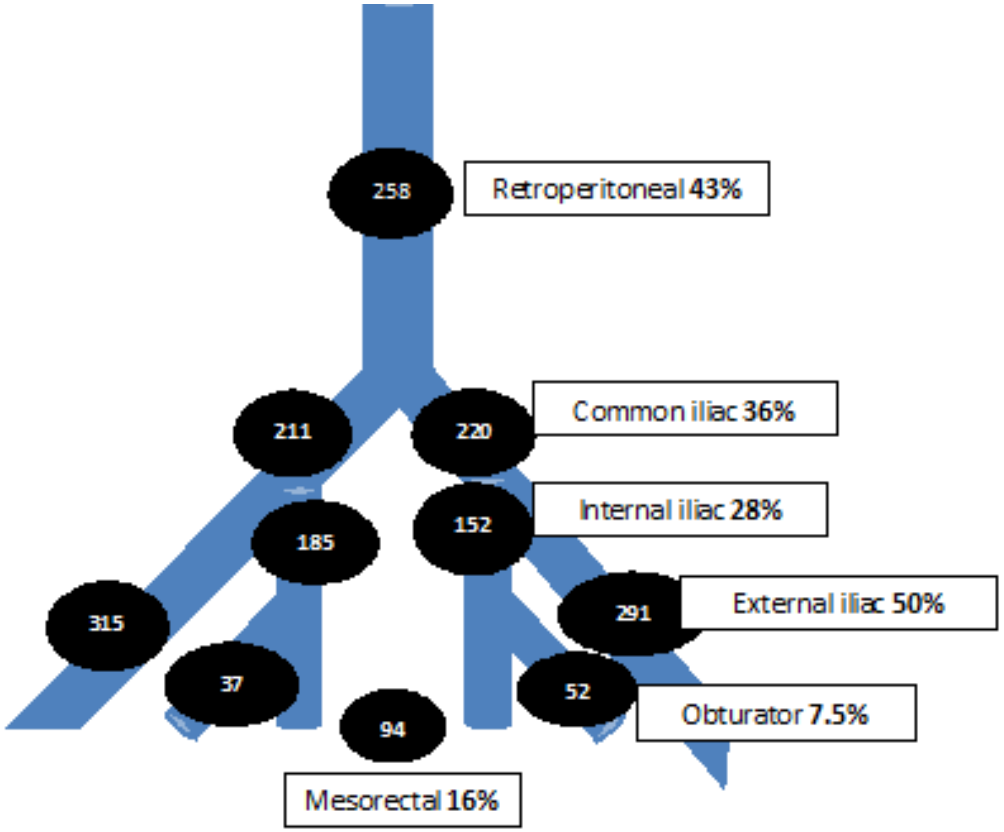




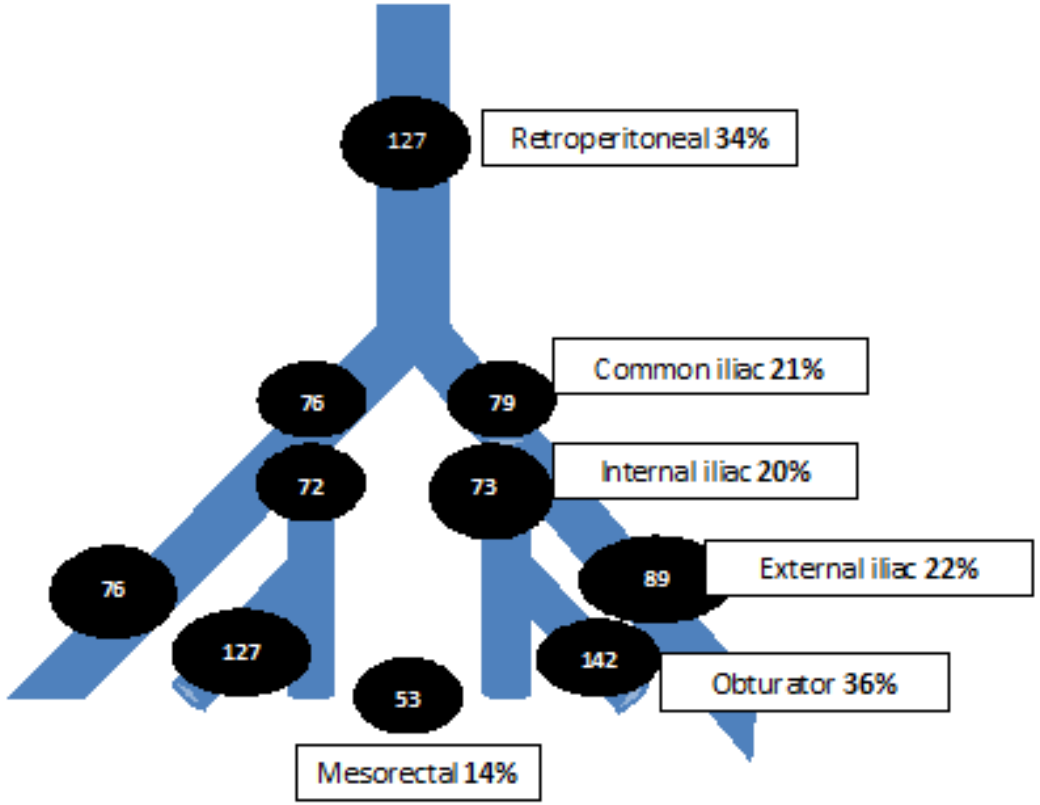
Haran et al, data submitted

Distribution of regional and non-regional nodal metastases

Abiraterone Comparison (602 pts)

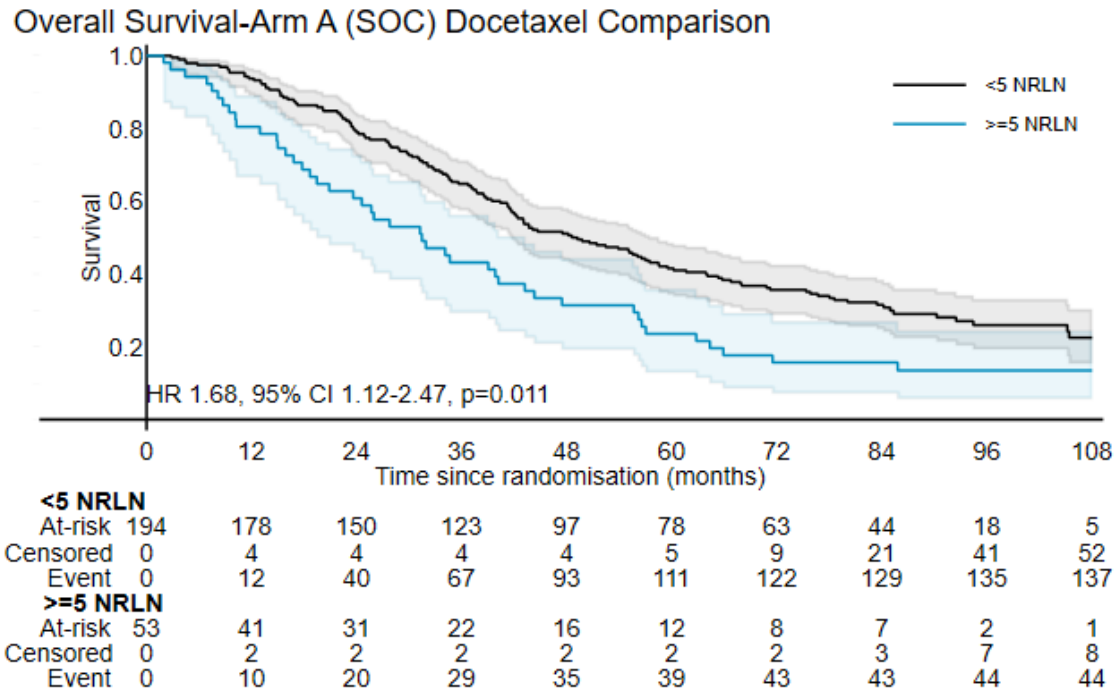


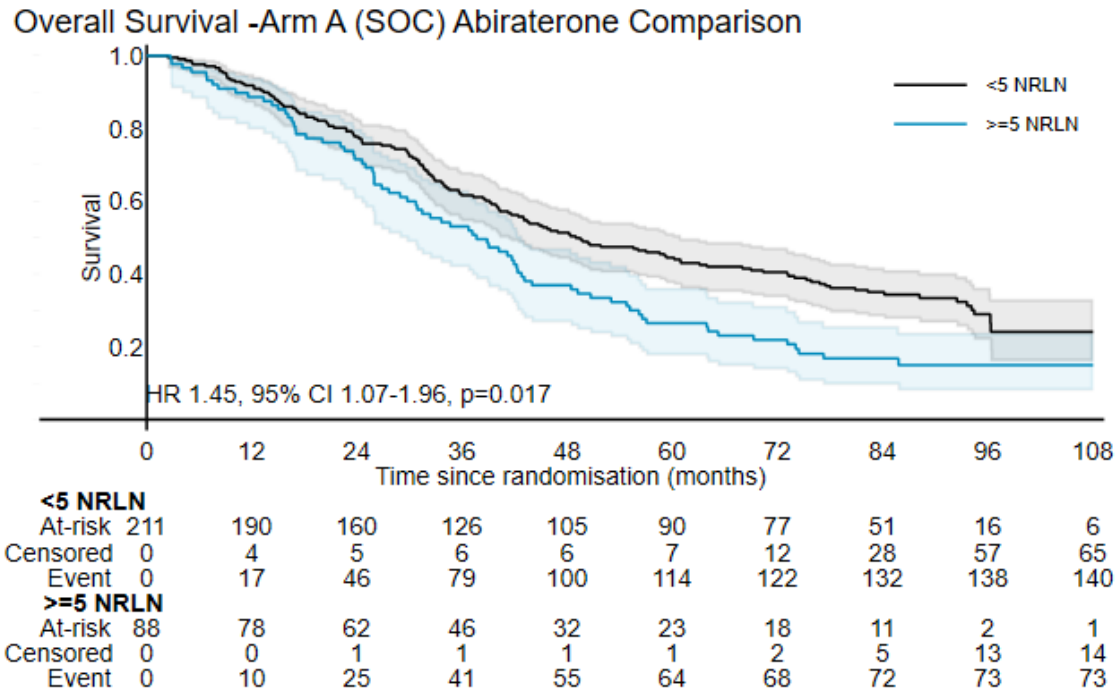
Docetaxel Comparison(373 pts)



Haran et al, data submitted

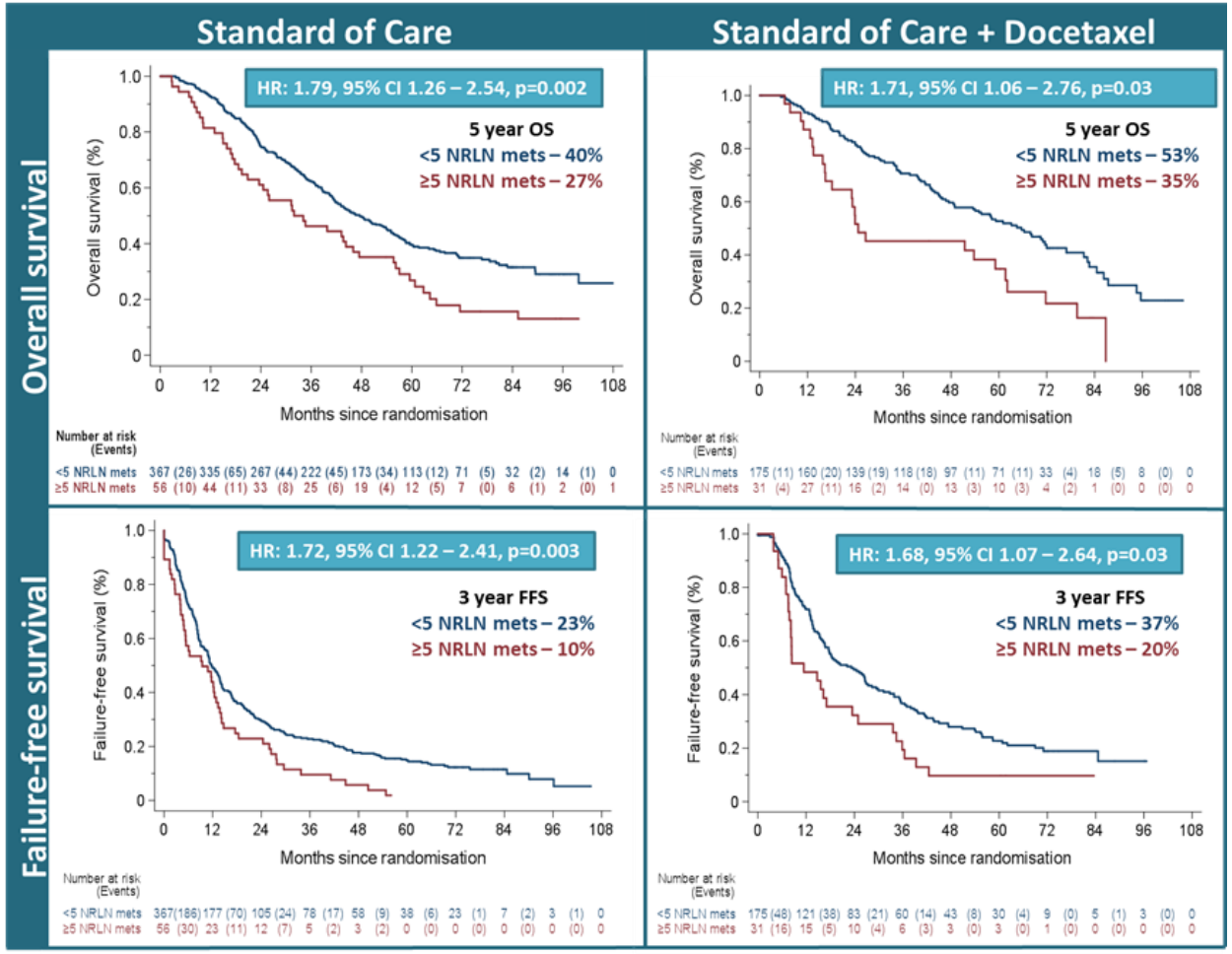
Nodal burden as a prognostic biomarker for worse OS in the control arms
-significant response in both arms
HR adjusted for Gleason score, bone mets, nstage, CHAARTED high/low , RT, age<70,≥70, WHO PS, nsaid/aspirin use





Haran et al, data submitted

The importance of lymph node location, burden and treatment outcome in M1 HSPC: analysis from the STAMPEDE trial Arms A & C



- 5yr Kaplan-Meier (KM) estimated OS of 27% for ≥5 NRLN vs 40% for <5NRLN (control group)
- 5yr KM estimated OS of 35%for ≥5 NRLN vs 53% for <5NRLN (docetaxel group)
- Increased NRLN burden at baseline associated with worse prognosis for M1 HSPC patients treated SOC or SOC and docetaxel
- NRLN metastases should be included in future risk/volume definitions

Hazard ratios obtained from multivariable Cox regression model adjusted for Age (*<70 or ≥70*), Performance status (*0 or 1-2*), Regional Nodal status (*N0, N1 or NX*), Concomitant metastatic site (*Only NRLN or Only Bone or Any Visceral/Other (+/-Bone*), NSAID or aspirin use (*Uses either or no*)

Haran et al AUA 2020 https://www.auajournals.org/doi/abs/10.1097/JU.0000000000000913.04

Relationship between metastasis number and RT effect

Research

JAMA Oncology | Original Investigation

Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer

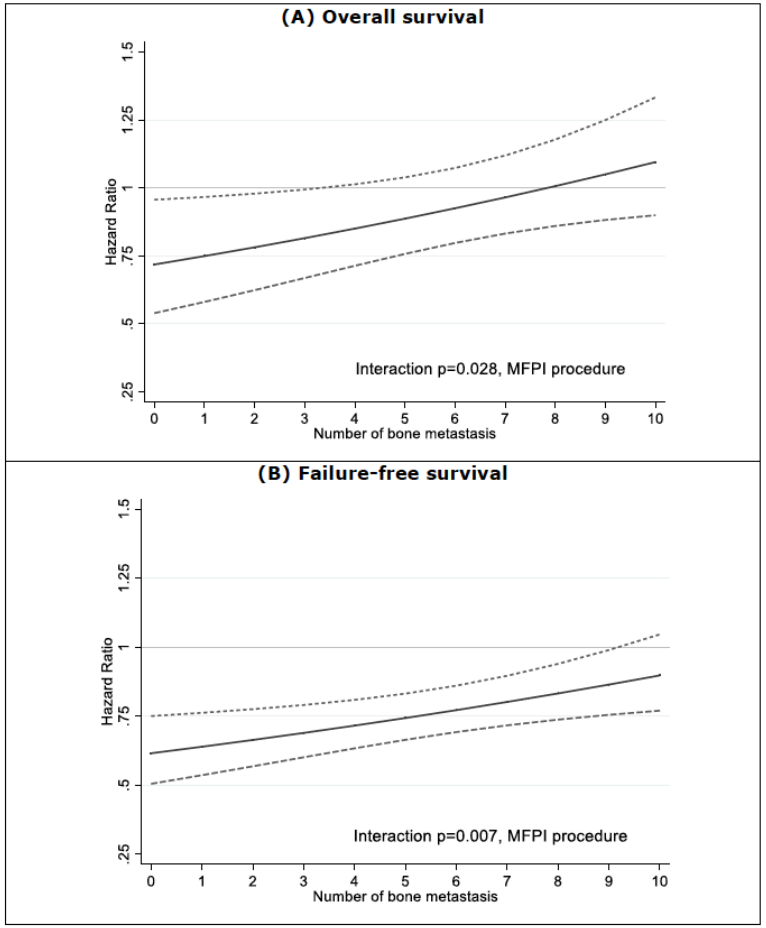
A Secondary Analysis of a Randomized Clinical Trial

Adnan Ali, MBBS; Alex Hoyle, MBBS, MRCS, MD; Áine M. Haran, MRCS; Christopher D. Brawley, MSc; Adrian Cook, MSc; Claire Amos, PhD; Joanna Calvert, MSc; Hassan Douis, PhD; Malcolm D. Mason, MD; David Dearnaley, MA, MD; Gerhardt Attard, MD, PhD; Silke Gillessen, MD; Mahesh K. B. Parmar, DPhil; Christopher C. Parker, MD; Matthew R. Sydes, MSc; Nicholas D. James, MBBS, PhD; Noel W. Clarke, MBBS, ChM

IMPORTANCE Prostate radiotherapy (RT) improves survival in men with low-burden metastatic prostate cancer. However, owing to the dichotomized nature of metastatic burden criteria, it is not clear how this benefit varies with bone metastasis counts and metastatic site.

Invited Commentary page 563

Supplemental content



Ali, A; Hoyle, A, Haran, A et al: JAMA Oncol 2021 DOI: 10.1001/jamaoncol.2020.7857

Relationship between metastasis number and RT effect

Research

JAMA Oncology | Original Investigation

Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer

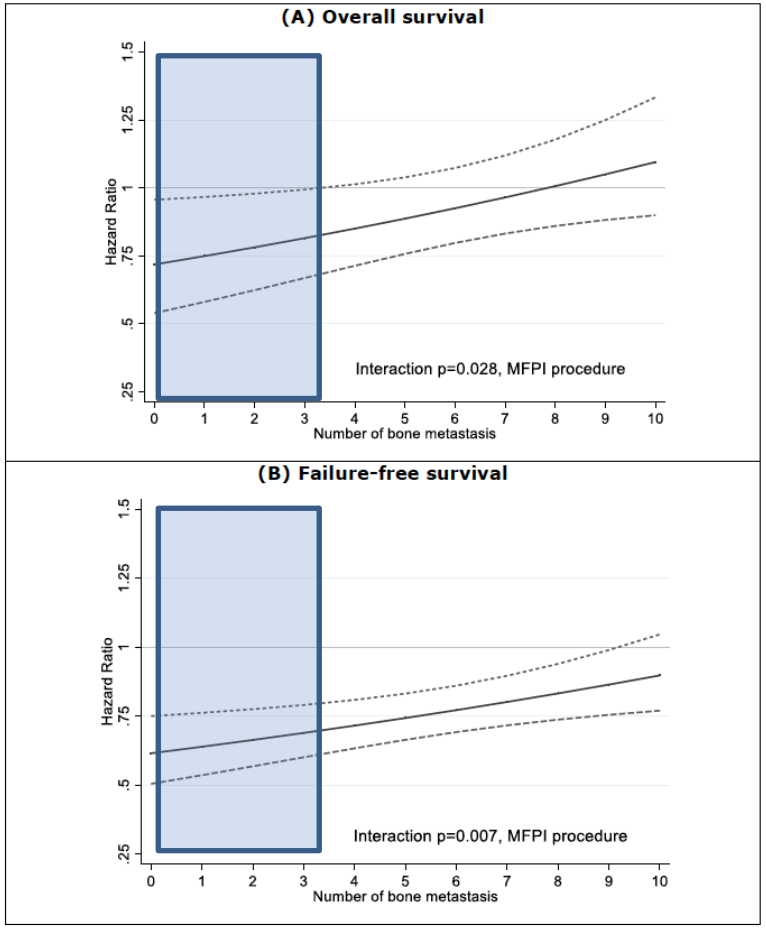
A Secondary Analysis of a Randomized Clinical Trial

Adnan Ali, MBBS; Alex Hoyle, MBBS, MRCS, MD; Áine M. Haran, MRCS; Christopher D. Brawley, MSc; Adrian Cook, MSc; Claire Amos, PhD; Joanna Calvert, MSc; Hassan Douis, PhD; Malcolm D. Mason, MD; David Dearnaley, MA, MD; Gerhardt Attard, MD, PhD; Silke Gillessen, MD; Mahesh K. B. Parmar, DPhil; Christopher C. Parker, MD; Matthew R. Sydes, MSc; Nicholas D. James, MBBS, PhD; Noel W. Clarke, MBBS, ChM

IMPORTANCE Prostate radiotherapy (RT) improves survival in men with low-burden metastatic prostate cancer. However, owing to the dichotomized nature of metastatic burden criteria, it is not clear how this benefit varies with bone metastasis counts and metastatic site.

Invited Commentary page 563

Supplemental content



Ali, A; Hoyle, A, Haran, A et al: JAMA Oncol 2021 DOI: 10.1001/jamaoncol.2020.7857

Can we automate the volume assessment?

EUROPEAN UROLOGY ONCOLOGY 3 (2020) 412–419

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

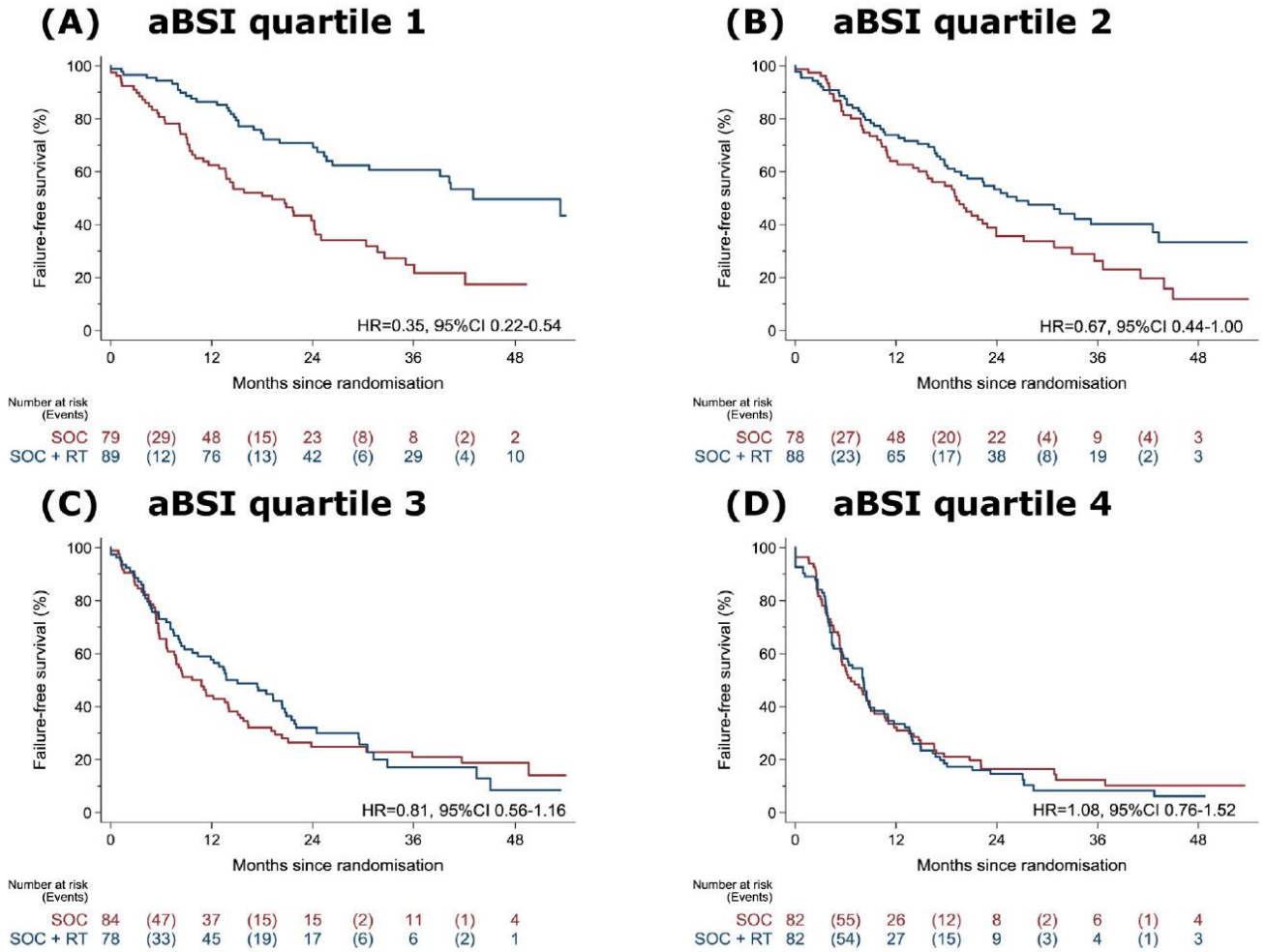
European Association of Urology

Priority Article

The Automated Bone Scan Index as a Predictor of Response to Prostate Radiotherapy in Men with Newly Diagnosed Metastatic Prostate Cancer: An Exploratory Analysis of STAMPEDE's "M1|RT Comparison"

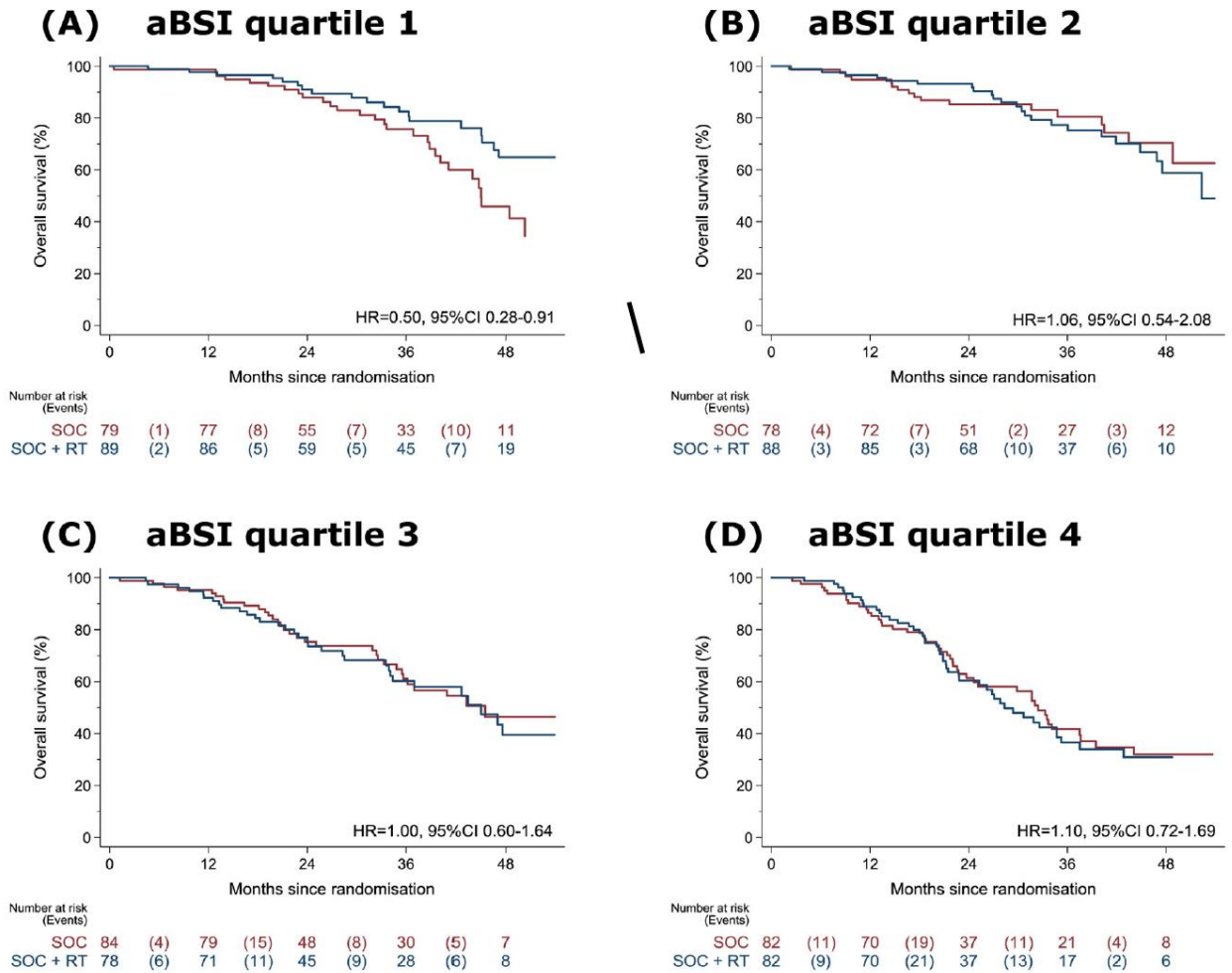
Adnan Ali [a,b,c], *Alex P. Hoyle* [a,b,c,d], *Christopher C. Parker* [e], *Christopher D. Brawley* [f], *Adrian Cook* [f], *Claire Amos* [f], *Joanna Calvert* [f], *Hassan Douis* [g], *Malcolm D. Mason* [h], *Gerhardt Attard* [i], *Mahesh K.B. Parmar* [f], *Matthew R. Sydes* [f], *Nicholas D. James* [e], *Noel W. Clarke* [a,b,c,d,*], *on behalf of the STAMPEDE investigators*

BSI uptake versus outcome – failure free survival



Ali, A; Hoyle, A, Haran, A et al: Eur Urol Oncol 2020 DOI: 10.1016/j.euo.2020.05.003

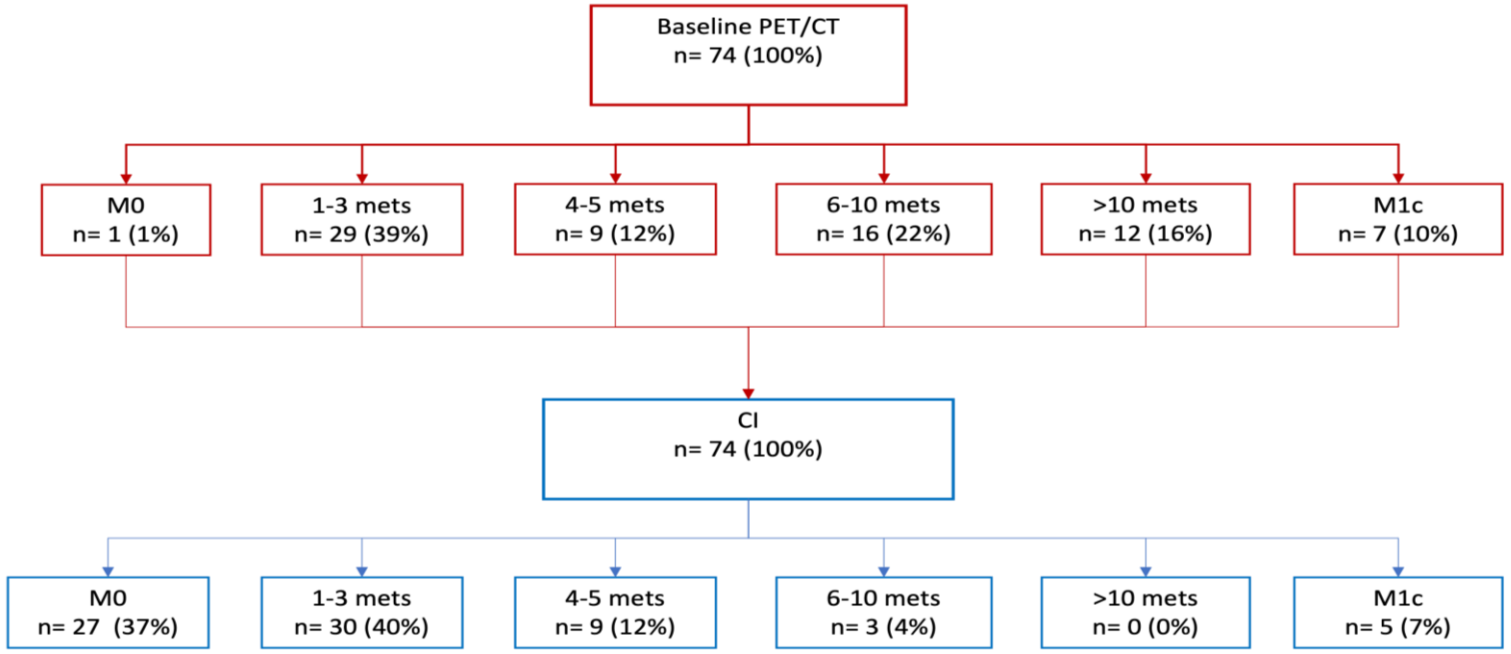
BSI uptake versus outcome – overall survival

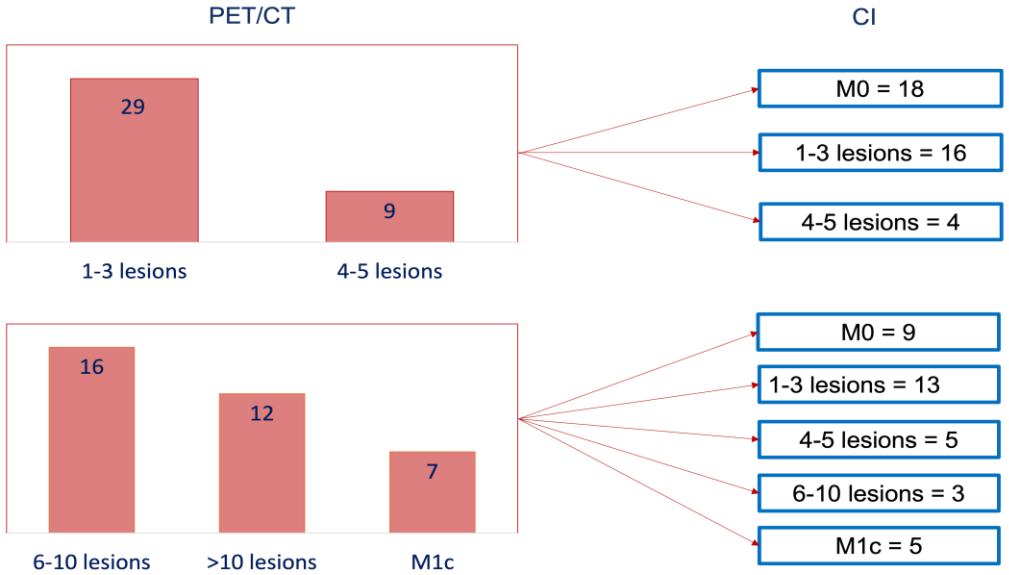


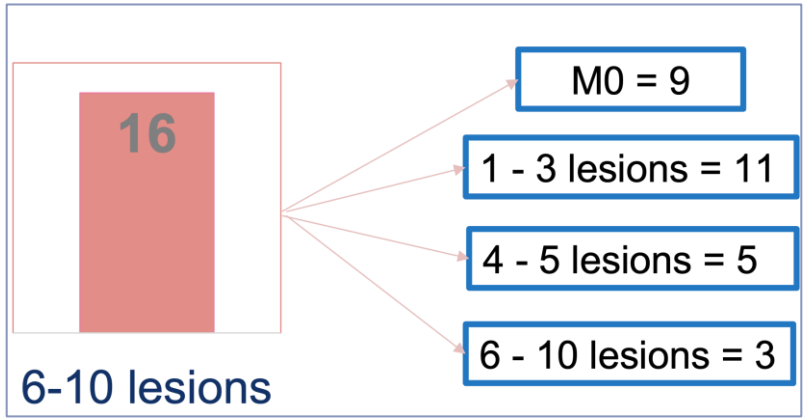
Ali, A; Hoyle, A, Haran, A et al: Eur Urol Oncol 2020 DOI: [10.1016/j.euo.2020.05.003](https://doi.org/10.1016/j.euo.2020.05.003)

Volume effects and radiotherapy

- No clear cutoff at 3 vs 4 metastasis
- Benefit extends to higher “oligometastatic” burden but difficult to define in era of PET imaging







62.5% OMD on CI
31% M0 on CI

Abdel Aty, Van As, James, unpublished

If benefit confined to low burden disease, can we irradiate all of it?

- PEARLS trial (in two parts)
  - M1a patients: Prostate only RT vs Prostate + nodal irradiation to include PA nodes
- STAMPEDE 2 – oligomets
  - Newly diagnosed HSPC with up to 5 metastases
  - Prostate (+/- pelvic nodes) RT vs Prostate (+/- pelvic nodes) RT + SABR to all metastases
- Range of other SABR trials in oligometastatic setting

Conclusions

- Benefit from local RT to prostate in low burden disease
- Complex relationship between burden as defined in CHAARTED and outcomes
- Raises possibility that some metastatic disease might be curable and this is being assessed in trials