



IS THE EXTERNAL BEAM REQUIRED IN INTERMEDIATE RISK DISEASE? LDR v LDR + EBRT

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WHAT IS THE AIM OF THE EBRT?

EBRT

- Increased dose than either individually
- Massage out cold spots
- SV coverage
- Nodal coverage

LDR

- mpMRI and targeted biopsy greater tumour identification
- Peri-prostatic coverage helped by stranded seeds
- 150-200% dose to tumour – high BED



SOME LEVEL 1 EVIDENCE TO HELP US

Initial Report of NRG Oncology/RTOG 0232: A Phase III Study Comparing Combined External Beam Radiation and Transperineal Interstitial Permanent Brachytherapy with Brachytherapy Alone for Selected Patients with Intermediate Risk Prostatic Carcinoma

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BACKGROUND 2003



- Intermediate risk patients were treated by XRT alone or in combination with brachytherapy but not brachytherapy alone
- Hypothesis is that patients treated by XRT + brachytherapy will have 10% improvement in FFP @ 5 years compared to brachytherapy alone



ELIGIBILITY CRITERIA

- T1-T2b
- PS 0-1
- One of the following
 - Gleason 2-6 and PSA ≥ 10 and < 20
 - Gleason 7 and PSA < 10
- Prostate volume $< 60\text{cc}$
- No prior ADT < 2 or > 6 months prior to randomisation
- IPSS < 16
- No metastases or suspicious nodes



RTOG 0232: STUDY SCHEMA

S T R A T I F Y	<u>Stage</u>	R E C O R D	<u>Isotope</u>	R A N D O M I Z E
	1. T1c 2. T2a – T2b			
	<u>Gleason Score</u>			
	1. ≤ 6 2. 7			
	<u>PSA</u>			
	1. < 10 2. 10-20			
	<u>Neoadjuvant Hormonal Therapy</u>			
	1. No 2. Yes			

89%

RADIATION PLANNING AND DOSES

- External Beam- Prostate & SV , nodes optional
- $PTV = CTV + 0.5-1.0\text{cm}$
- Dose $PTV > 98\%$, 25# of 1.8Gy to 45Gy
- 43% IMRT
- Brachytherapy 2-4 weeks later
- PTV defined by TRUS and $PTV = CTV + 2-5\text{mm}$

Dose	I-125 (482)	Pd-103 (81)
Monotherapy	145 Gy	125 Gy
Boost	110 Gy	100 Gy
Source Activity	.277 - .548 U	1.29 - 2.61 U



RTOG 0232 ACCRUAL SUMMARY

Date activated	6/11/2003
Date closed	2/8/2012
Target sample size	586

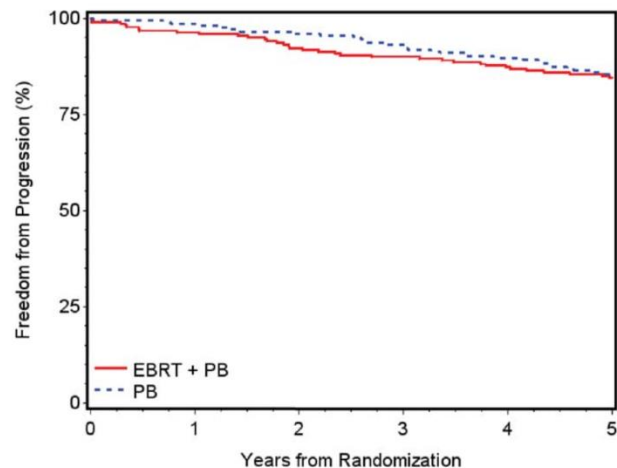
	EBRT + PB	PB	Total
Randomized	292	296	588
Ineligible	5	4	9
Eligible	287	292	579



RESULTS -FREEDOM FROM PROGRESSION

EBRT & Brachytherapy 85% @5yrs

Brachytherapy alone 86% @5yrs



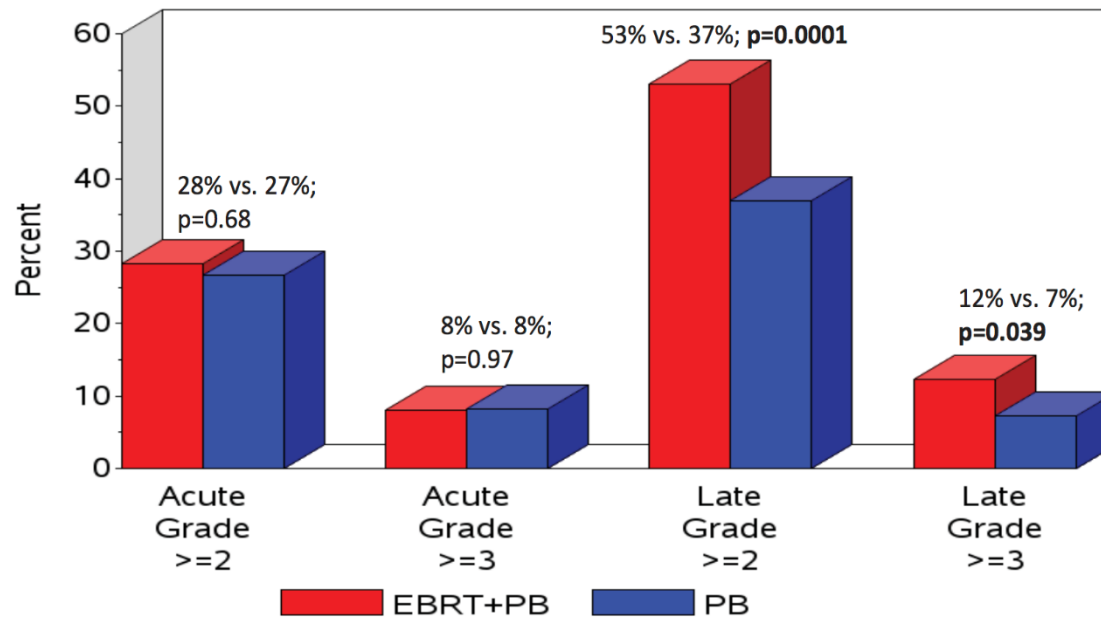
Patients at Risk						
EBRT + PB	220	212	203	198	192	183
PB	223	219	213	207	198	186

First Failure	EBRT + PB (n=34)	PB (n=32)	Total (n=66)
BF-ASTRO	23 (68%)	17 (53%)	40 (61%)
LP	1 (3%)	1 (3%)	2 (3%)
LP, DM	1 (3%)	0 (0%)	1 (2%)
Death*	9 (26%)	14 (44%)	23 (35%)

ADVERSE EVENTS

Late grade 2 & 3 AE's significantly greater with combination

Especially increased GU toxicity 7% v 3%



CONCLUSIONS- TRIAL COMMENTS

- Among men with intermediate risk prostate cancer the addition of external beam to brachytherapy **did not** result in superior freedom from progression compared to brachytherapy alone at 5 years
- Toxicity was limited for both groups however **fewer late effects (mostly GU 3% v 7%) with brachytherapy alone**
- Implications for practice: **men with intermediate risk may well be managed by brachytherapy alone**
- Sub set analysis required to assess if true for unfavourable intermediate risk patients
- Longer FU required to make sure of durability of findings



MY CONCLUSIONS



EBRT & Brachytherapy for
favourable intermediate risk
disease

Increased gas
and rectal
problems



MY CONCLUSIONS



EBRT & Brachytherapy for favourable
intermediate risk disease



Increased gas
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Increased
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MY CONCLUSIONS



EBRT & Brachytherapy for favourable intermediate risk disease

Increased gas and rectal problems



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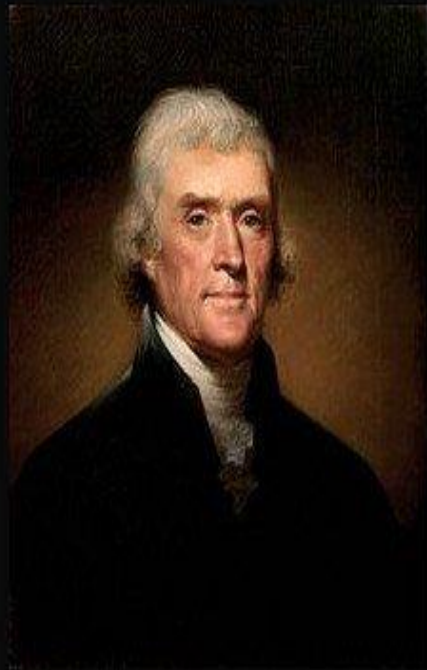
Can land you in trouble



WHAT WE NEED IS BETTER PATIENT STRATIFICATION



IMMORTAL DECLARATION- DECLARATION OF INDEPENDENCE - 1776



We hold these truths to be self-evident: that all men are created equal; that they are endowed by their Creator with certain unalienable rights; that among these are life, liberty, and the pursuit of happiness.

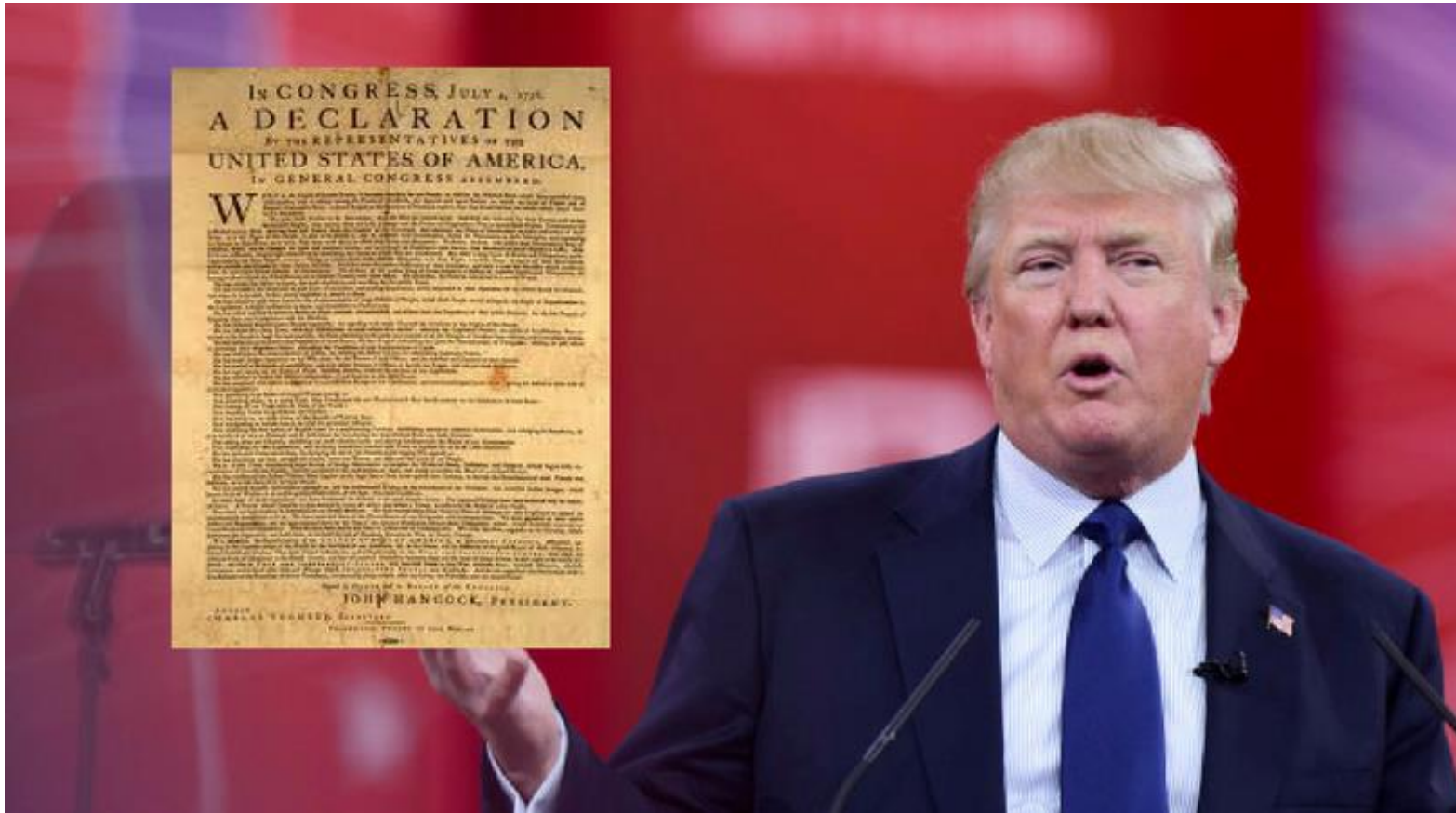
(Thomas Jefferson)

izquotes.com



TRUMP IN 2009: 'ALL MEN ARE CREATED EQUAL' IS 'A VERY CONFUSING PHRASE'

DAVID BIXENSPAN FOX NEWS | 12:16 PM, JANUARY 17TH, 2017



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THEY ARE ALL SPIDERS BUT WHICH ONES CAN KILL YOU?


if bitten by a **FUNNEL-WEB** or a **MOUSE SPIDER**: apply pressure immobilisation bandage and **call 000** for an ambulance
if bitten by a **RED-BACK SPIDER**: apply cold pack to bite and go to the nearest hospital

DEADLY & DANGEROUS


Female to 15mm
Male to 20mm
long spinnerets

Sydney Funnel-Web
one of the world's deadliest spiders
ground dwelling • aggressive during summer/autumn



Female to 14mm
Male to 3mm

Red-Back
fatal bites recorded
found under houses, rocks, logs, rubbish, etc.





Female to 20mm
Male to 12mm
small spinnerets

Mouse Spider
deep painful bite • often mistaken for a funnel-web
ground dwelling • wander after rain


If bitten by one of these spiders below, apply a cold pack to relieve pain.
If symptoms persist, seek medical attention.

PAINFUL BITE


Female to 18mm
Male to 8mm

Common Black House Spider
venomous • nervous, terrifying, etc.
often found around window frames, fences, eaves, etc.



Female to 25mm
Male to 30mm



Wolf Spider
non aggressive
ground dwelling • often found in lawns



Female to 20mm
Male to 25mm


White-Tail Spider
may result in local ulceration to skin
commonly found inside homes

LOW RISK


Female to 15mm
Male to 10mm

Trap Door
mildly toxic • non aggressive
often mistaken for a funnel web • ground dwelling • burrow




Female to 20mm
Male to 20mm

Garden Orb-Weaving
relatively harmless • beneficial
found in the garden suspended on sticky webs



Female to 30mm
Male to 30mm

Saint Andrew's Cross
harmless • beneficial
found in the garden suspended on sticky webs



Female to 40mm
Male to 30mm

Huntsman
timid • seldom bites
found under bark & leaf litter • wanders indoors

If bitten, try to catch the spider (if safe to do so) for correct identification.

RECENT PUBLICATION



RESEARCH ARTICLE

Improving Clinical Risk Stratification at Diagnosis in Primary Prostate Cancer: A Prognostic Modelling Study

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Study Cohort split 60:40 training v validation

Table 1. Distribution of the primary study cohort ($n = 10,139$) by age, PSA at presentation, biopsy grade, and clinical stage.

Clinico-pathological Characteristic		n
Age (y)		
<60		1,121
60–69		3,717
70–79		4,012
≥ 80		1,289
PSA (ng/ml)		
<10		4,118
10–20		3,306
>20		2,715
Biopsy grade/ISUP prognostic score		
≤3 + 3/prognostic score 1		3,411
3 + 4/prognostic score 2	ISUP grade Grouping = prognostic score	2,991
4 + 3/prognostic score 3		1,503
8/prognostic score 4		1,004
9–10/prognostic score 5		1,230
Stage		
T1		5,452
T2		3,226
T3		1,384
T4		77

Creation of 5 risk groups

Table 2. Proposed new prostate cancer risk stratification system.

New Risk Group	Criteria
1	Gleason 6 (prognostic score 1) AND PSA < 10 ng/ml AND Stage T1–T2
2	Gleason 3 + 4 = 7 (prognostic score 2) OR PSA 10–20 ng/ml AND Stage T1–T2
3	Gleason 3 + 4 = 7 (prognostic score 2) AND PSA 10–20 ng/ml AND Stage T1–T2 OR Gleason 4 + 3 = 7 (prognostic score 3) AND Stage T1–T2
4	Any one of Gleason 8 (prognostic score 4) OR PSA > 20 ng/ml OR Stage T3
5	More than one of Gleason 8 (prognostic score 4), PSA > 20 ng/ml, Stage T3 OR Any Gleason 9–10 (prognostic score 5) OR Any Stage T4

The prognostic scores refer to the new ISUP classification [11].



Better PCSM discrimination than NICE

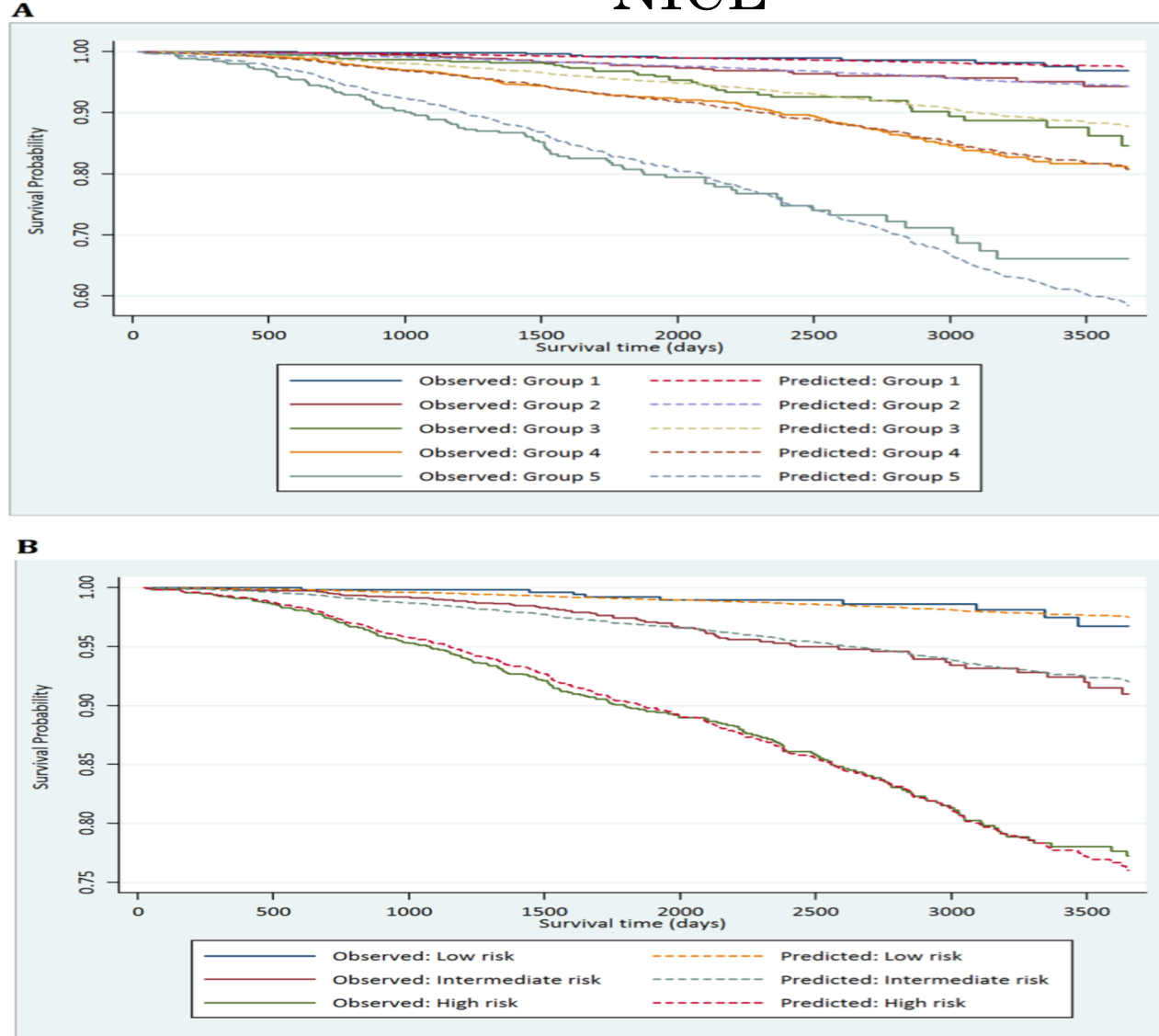


Fig 3. Calibration plots of the risk groups. (A) Calibration curves for prostate-cancer-specific survival using the new risk stratification system applied to the testing set ($n = 4,113$). (B) Model calibration set curves for prostate-cancer-specific survival using the NICE risk stratification system applied to the testing set.

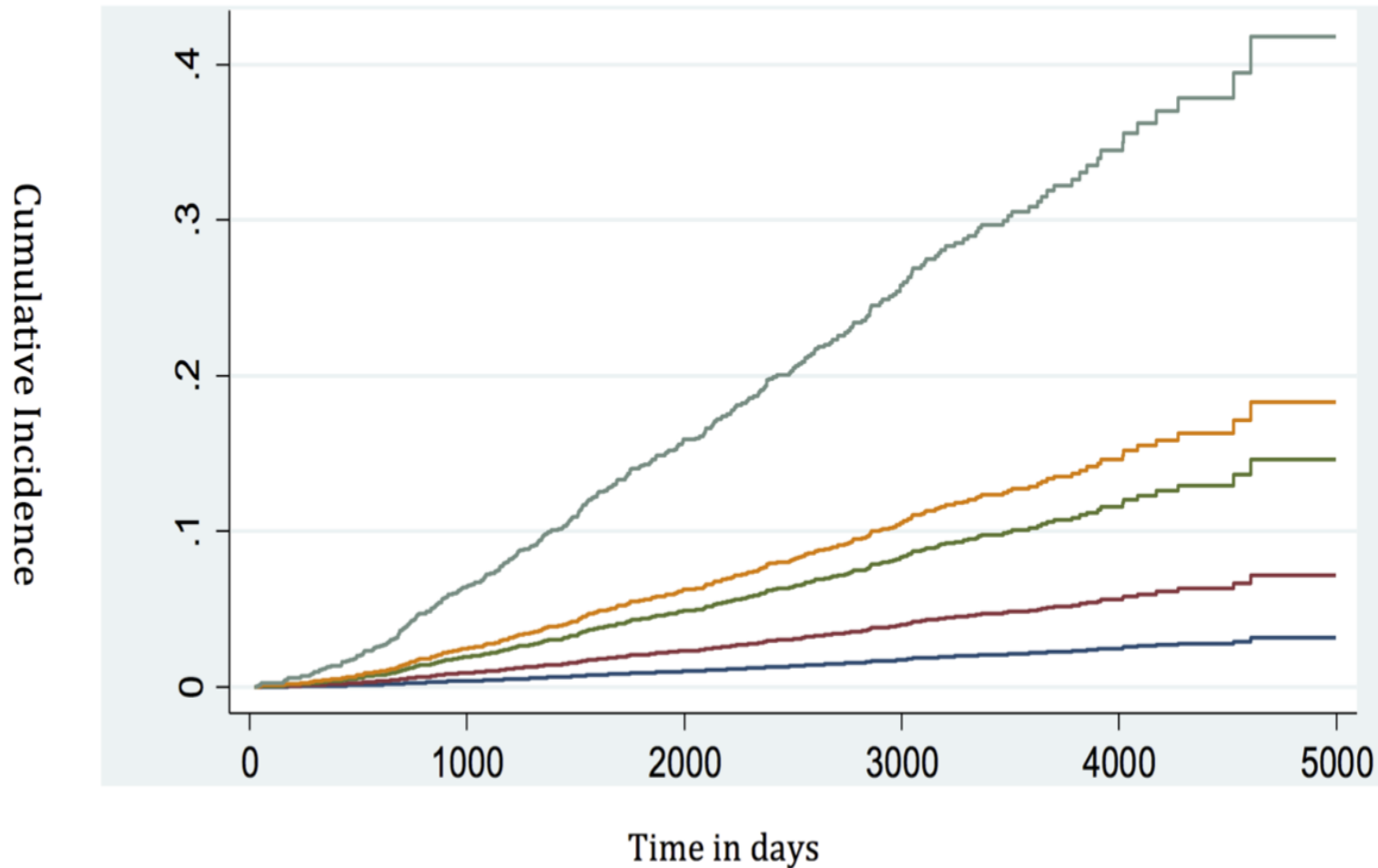


Fig 4. Cumulative incidence curves applied in the testing set to assess the competing mortality risks in the new model.

Real world validation; simple stratification to use in UK unscreened population

Table 5. Competing-risks regression analysis of the new risk model in the testing set.

Risk Group Comparison	HR	95% CI	p-Value
1 versus 2	2.35	1.15–4.81	0.019
2 versus 3	2.18	1.35–3.52	0.001
3 versus 4	1.51	1.08–2.13	0.017
4 versus 5	2.24	1.73–2.89	<0.0001

Intergroup comparisons are shown, demonstrating clear differences in outcome between groups.

Table 6. Concordance indices of the NICE stratification system and the new risk model for prostate-cancer-specific mortality, with inclusion of competing risks, in the testing cohort and external validation cohort ($p < 0.0001$ for both comparisons).

Cohort (n)	Concordance Index (95% CI)	
	NICE Stratification System	New Risk Model
Testing set (4,113)	0.69 (0.66–0.71)	0.75 (0.72–0.77)
Validation cohort (1,706)	0.66 (0.63–0.69)	0.79 (0.75–0.84)



HOW TO IMPROVE IT FURTHER

- Inclusion of mpMRI staging (PSMA-PET)
- Image guided biopsies
 - Improved staging/ cancer detection
- Include all cause mortality not just PCSM via age and co-morbidity stratifications
 - Competing risk v benefits of treatment
- Molecular signatures
 - gene signatures , 17, 22, 30, 40 etc
 - Commercially available (Decipher, Oncotype DX, Polaris)
 - Concordance Index very similar to above 0.75-0.79 range



‘MAKE PATIENT SELECTION GREAT AGAIN’

