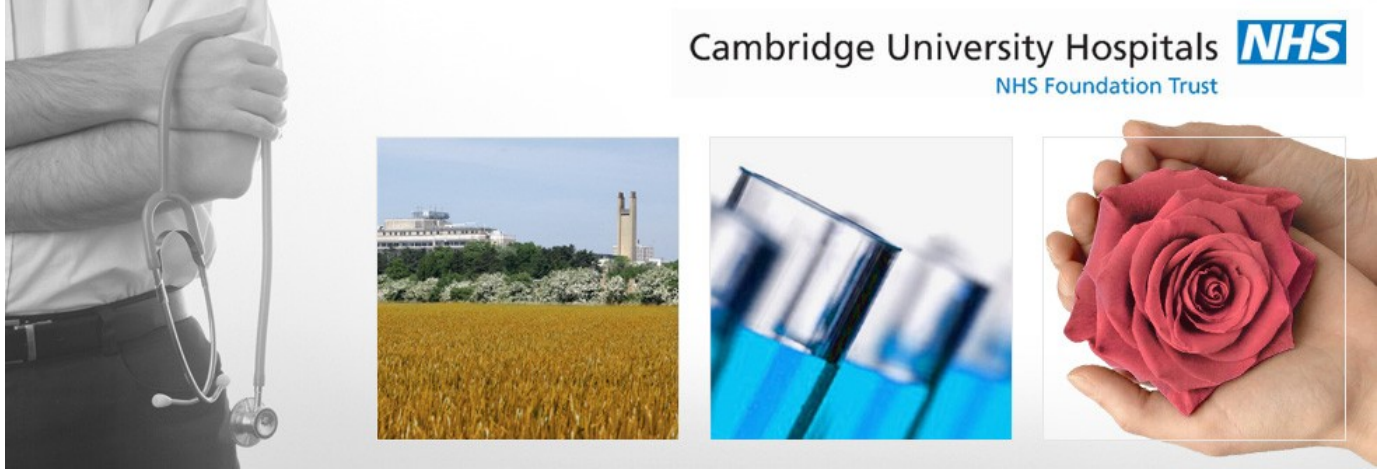

Clinical trials in Molecular Radiotherapy

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Introduction

- Look at the role of clinical trials in radionuclide therapy
- Understand some of the terms used in clinical trials
- Look at two recent examples
  - Commercial trial – Alpharadin
  - Academic trial - HiLo

Why clinical trials

- Provides evidence base for clinical practice
- Provides data for toxicity and efficacy which is required for consent
- Provides evidence for re-imbursement
- Enables nuclear medicine to compete with other treatment modalities

What is needed for success

Sir Chris Hoy 6 Gold medals in 5 sequential Olympics Atlanta 1996, Sydney 2000, Athens 2004, Beijing 2008, London 2012

What is needed for success

What team for clinical trials

- NM doc
- Oncologist
- Study nurse
- Physicist
- NM techs
- Sponsor
- Clinical trials cordinator

ECTD

- Most studies in Europe has to follow ECTD
- Defines roles and responsibilities
- Provides a quality mark for all involved
- Ensures any medicinal product complies with GMP
- Will allow studies done in different countries to have comparable results

GMP

- Good manufacturing practice
- Ensures quality of products used in trials
- Each component must come from a GMP source
- Any product must be made to GMP with all records kept of what was used and how it was put together

The protocol

- This is the method that must be completed by all those undertaking trial
- Defines inclusion and exclusion criteria
- Defines what treatments to be given and when
- Defines what tests will be done to identify efficacy and toxicity
- Type of protocol defined by stage of trial

Types of trials

- Pre-clinical will be needed for new agents
- Phase-1 Defines maximum tolerated dose and for radio-isotopes dosimetry. In oncology normally done on patients with advanced cancers up to 25 patients
- Phase-2. Tries to define efficacy limited number of centres with fixed activity or fixed dose can be up to 100 patients

Phase I Dose Escalation Schedule

No of Patients	Treatment	Dose increase
3	10 mg CHT-25 + 370 MBq/ m^2 ^{131}I	
3	10 mg CHT-25 + 740 MBq/ m^2 ^{131}I	X 2
3	* 10 mg CHT-25 + 1480 MBq/m^2 ^{131}I	X 2
3	* 10 mg CHT-25 + 2220 MBq/m^2 ^{131}I	X 1.5
3	* 10 mg CHT-25 + 2960 MBq/m^2 ^{131}I	X 1.3

* Bone Marrow Harvesting required

Administered activity in MBq/m² (actual administered activity)

Patient	#1	#2	#3	#4	Cumulative activity
1	370 (663)				370 (663)
2	370 (573)				370 (573)
3	370 (725)	740 (1377)			1110 (2102)
4	740 (1380)	1480 (1868)	2220 (3395)	370 (554)	4810 (7197)
5	740 (1286)	1480 (2220)			2220 (3506)
6	740 (1104)				740 (1104)
7	1480 (2397)	2220 (2560)	2960 (4553)		6660 (10507)
8	740 (1093)				740 (1093)
9	740 (1105)	1480 (2104)	2220 (3239)		4440 (6448)

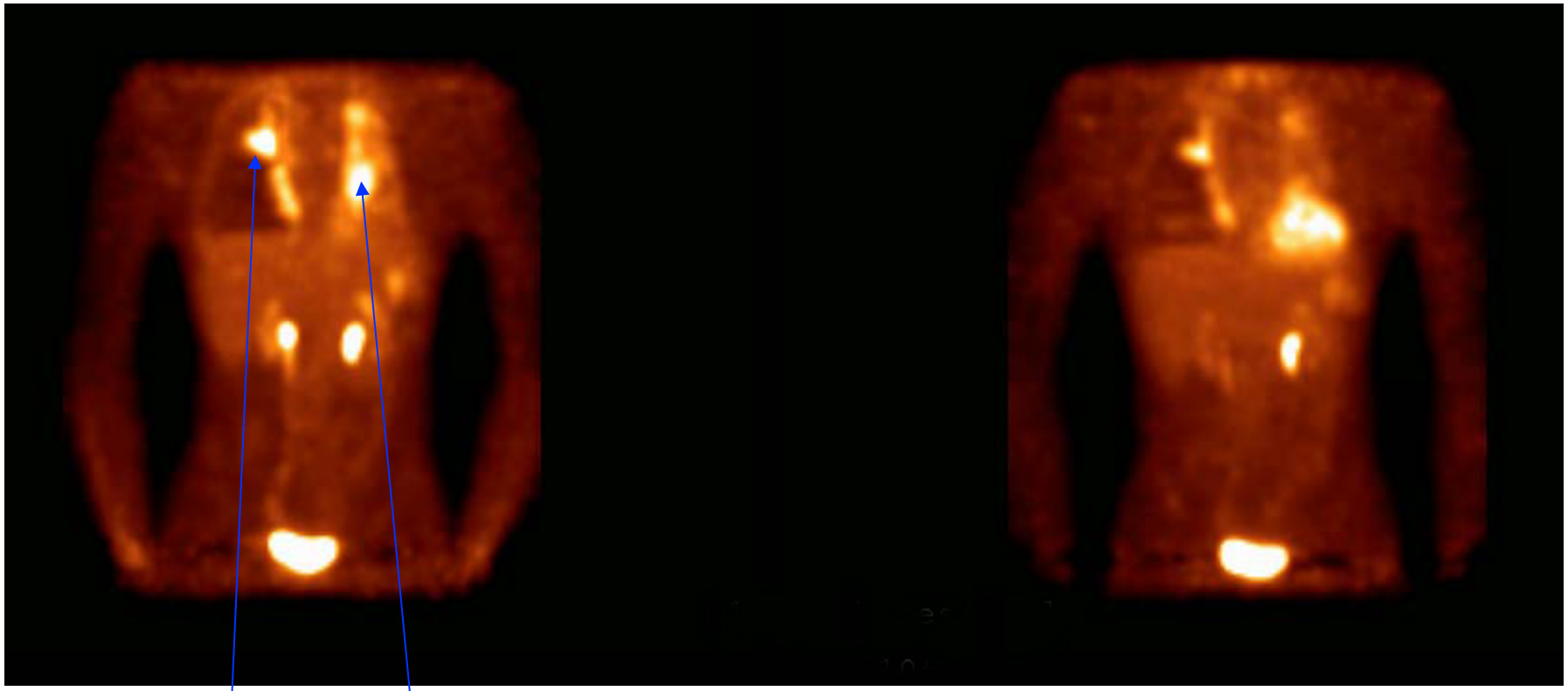
Repeated therapy possible at 1 month if localisation > 3% injected activity/kg + no stem cell rescue required

Incidence and CTC grade of haematological toxicity in relation to administered activity

Administered activity (MBq per m^2)	Treatment no.	Haemoglobin	Neutrophils	Lymphocytes	Platelets
370	4	G1(1),G2(2) G3(1)		G1(1),G2(1) **G3(2)**	G2(1) G3(1)
740	6	G1(1),G2(5)	G2(1)	**G3(4)**	G1(1) G2(1)
1480	4	G1(1),G2(2)	G1(2),G2(3) **G3(4)**	G2(1), **G3**(3)	**G3(2) G4(1)**
2220	3	G2(2), G4(1)	G2(1), **G3(1)**	**G3(3),G4(1)**	**G3(1) G4(2)**
2960*	1	G2	**G4**	**G3**	**G3**

*DLT with toxic death due to *pneumocystis* pneumonia

FDG-PET Response in Hodgkin's disease following 554 MBq (patient 04)



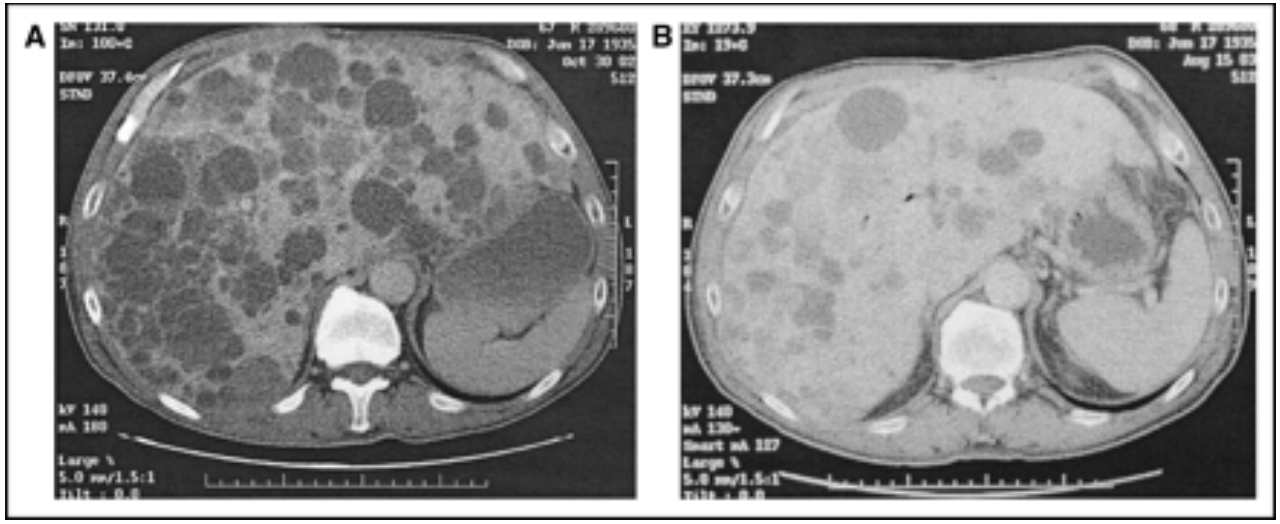
Phase II

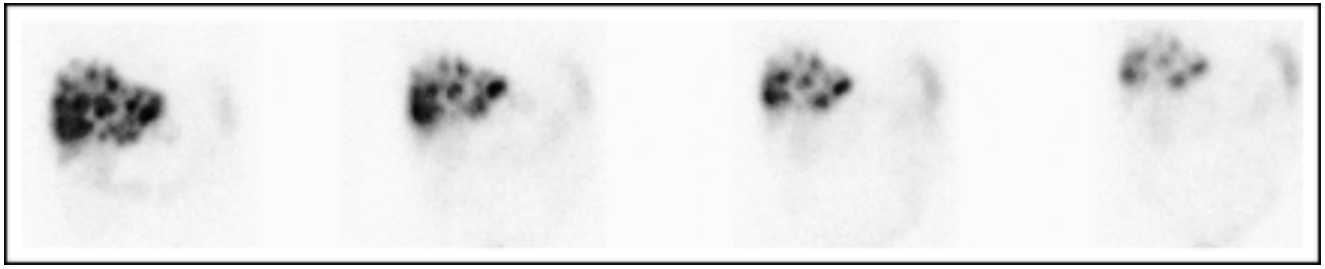
- Can be single centre or multi-centre
- Looks at marks of efficacy
- Should not be seen as final proof
- Sets up expected response rate
- This to be used to power a proper phase III that will provide proof of efficacy
- Still monitor toxicity

Lu-177 octreotate (n=310) Kwekkeboom JCO 2008

- Carcinoid n=188
  - 1% CR, 22% PR, 17% MR, 42% SD, 20%DP
- PET non func n=72
  - 6% CR, 36% PR, 18%MR, 26% SD, 14% DP
- PET func n=19
  - 0% CR 60% PR, 20% MR, 30% DS, 10% PD

Krenning et al JCO 2005





Phase III trials

- Compare 2 types of treatment
- Can be vs placebo or vs standard treatment
- Normally multicentre
- If for registration maybe paid for by a drug company
- If to determine best practice may be funded by government or charity
- Patients assigned randomly to the two groups
- Often patient and their doctors “blinded”

Trial oversight-1

- Trial committee
  - Made up of PI of trial, centre PIs and sponsor
  - Reviews recruiting
  - No access to un-blinded data
  - Responsible for ensuring data collected though this may be via a third party
  - Publishes results

Trial oversight - 2

- Independent Drug (Trial) Monitoring Committee
  - Not involved in trial but knowledge of trial
  - Reviews un-blinded data at pre-determined time points
  - Looks for safety issue
  - Can stop trial
    - Toxicity
    - Poor recruitment
    - Proven efficacy
  - Not a co-author on final paper

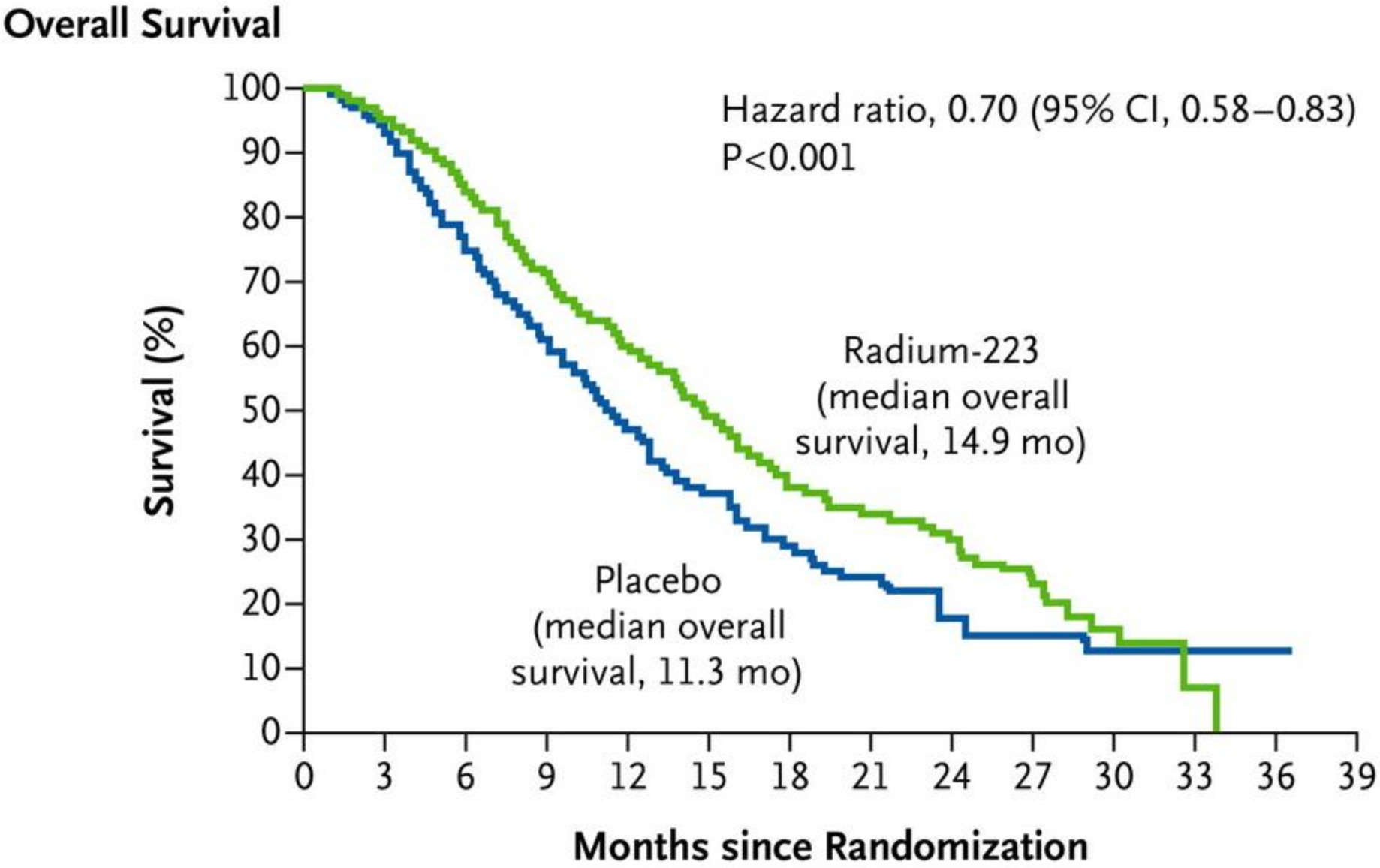
Alpharadin Phase III RCT

- Set up by Algeta/Bayer
- Based at Radium Hospital, Oslo
- Commercial interest from Bayer
- Plan to set up trial in 30 countries
- Powered to show survival
- Need 900 patients 2/3 to have treatment, 1/3 placebo
- No imaging to preserve blinding
- Published NEJM July 2013 369: 213 Parker et al

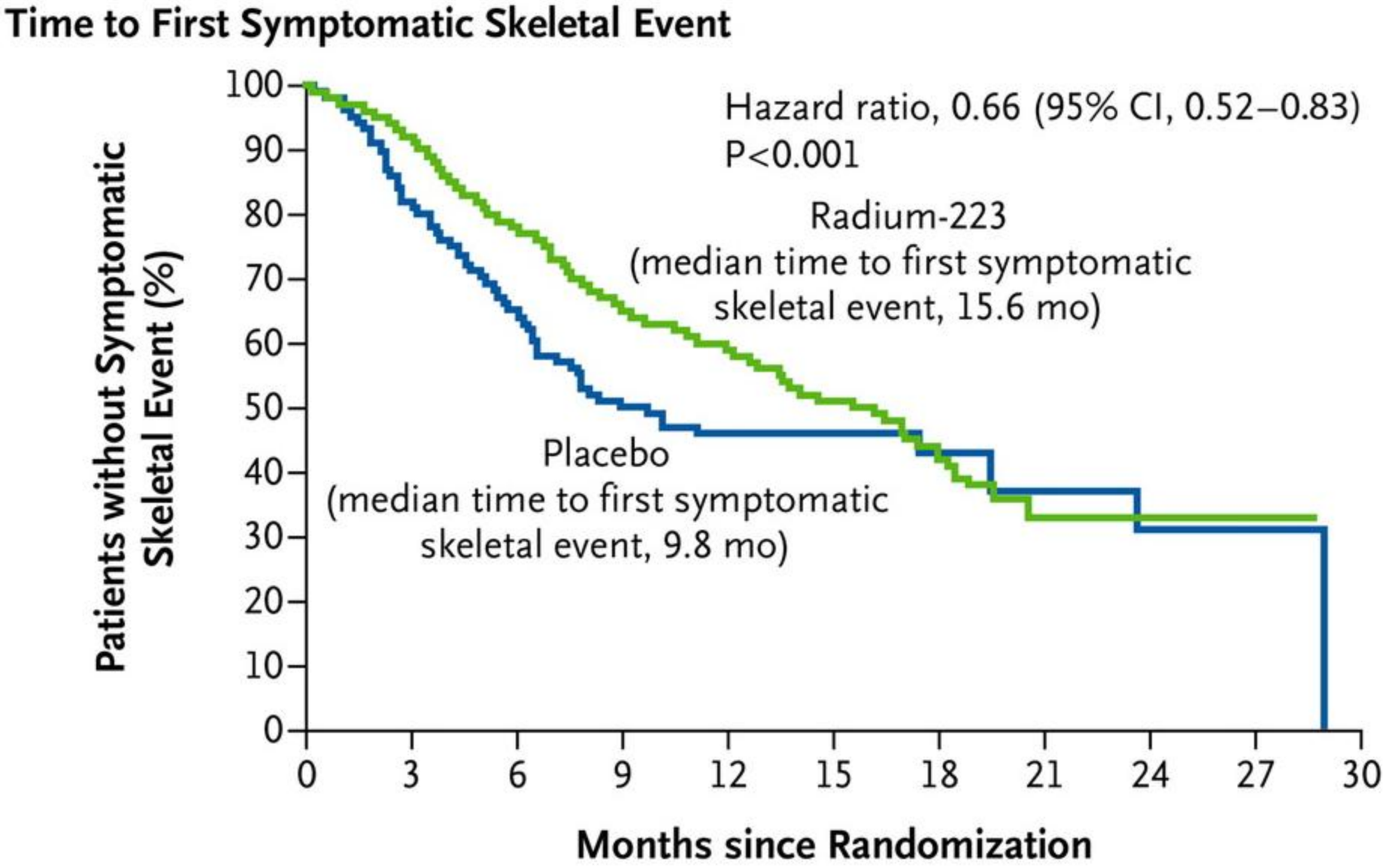
Protocol

- Patient to have proven bone metastases from Ca prostate
- Could have failed therapy such as taxanes
- After consent randomised to treatment or placebo
- Only one person at each sites know if it is active drug-must not tell patient or other docs
- 30kBq/kg 4 weekly for 6 cycles if live long enough or symptoms not worse

Results OS


Overall Survival
Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
27
30
33
36
39
Months since Randomization
Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001
Radium-223
(median overall
survival, 14.9 mo)
Placebo
(median overall
survival, 11.3 mo)

New bone pain



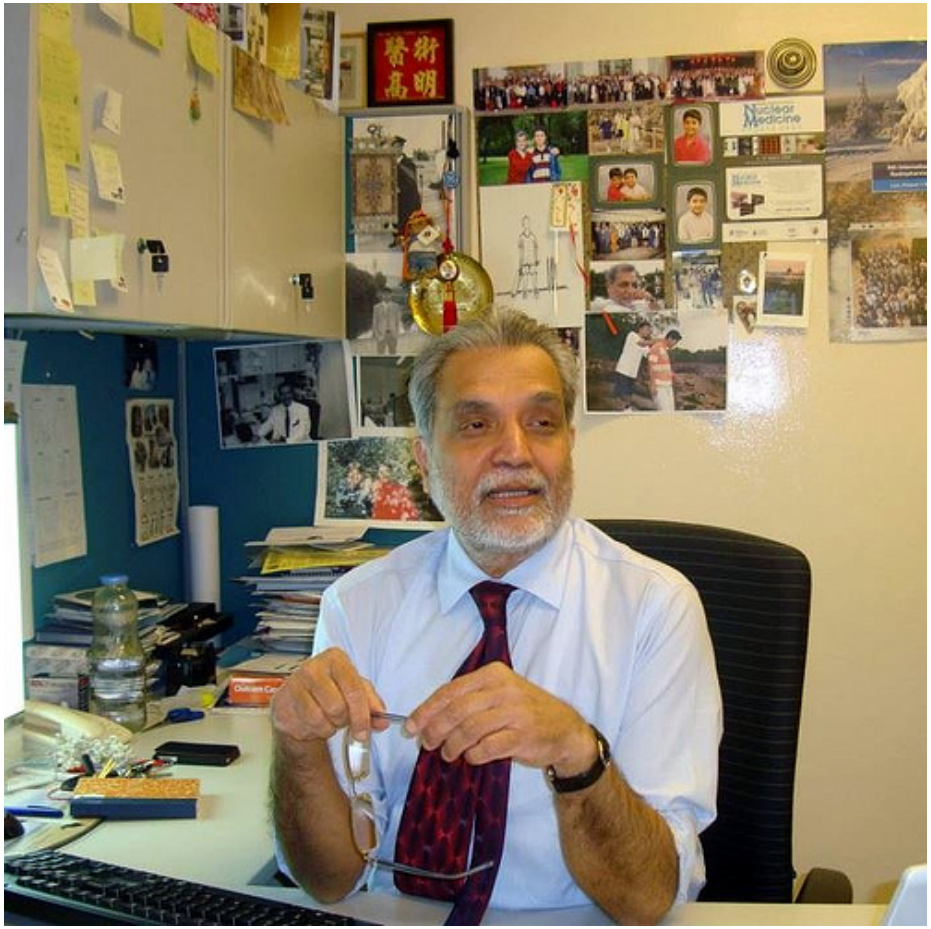
A different approach

- The treatment of thyroid cancer has been in the realm of nuclear medicine since 1940s
- I-131 remains the most widely used radioisotope in cancer 70 years later
- General plan total thyroidectomy then use I-131 to destroy all remaining thyroid tissue and then monitor patient using TBG
- Normally use 100mCi (3.7GBq I-131)

Thyroid cancer –question 1

- rTSH used instead of T4 withdrawl when imaging patients with low activity I-131 or I-123
- Been shown to produce images as good as T4 withdrawl
- Though often used before therapy no clinical trial and not licenced
- Was rTSH as good as withdrawl

Inspired by Prof Padhy



Prospective randomized clinical trial to evaluate the optimal dose of 131 I for remnant ablation in patients with differentiated thyroid carcinoma.
Bal C, Padhy AK, Jana S, Pant GS, Basu AK.Cancer. 1996 Jun 15;77(12):2574-80

Queation 2-How much I-131

- Though I-131 not expensive
- Activity too high to allow patients to be treated as an out-patient
- The main cost of treatment is the in-patient care
- Also the higher the activity the increased chance of side effects such as dry mouth
- Study from India suggested 1.1GBq is sufficient

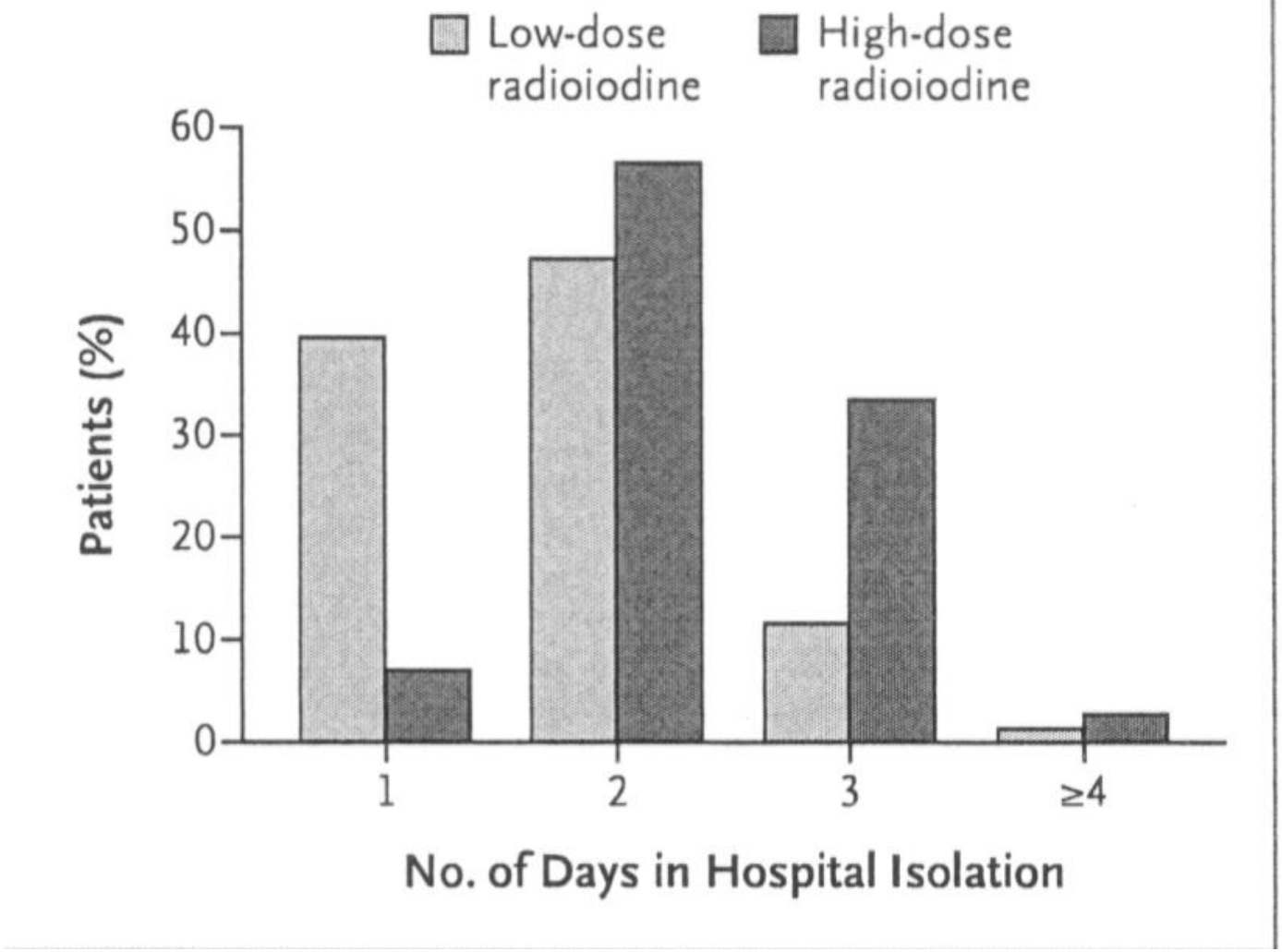
How to set up an RCT

- Two questions
  - Would 1.1GBq be as good as 3.7GBq in ablating the thyroid
  - Could rTSH be used to replace T4 withdrawl
- Company that makes rTSH may be intertested in funding part of study
- None of the companies making I-131 interested in selling LESS I-131

HiLo

- Put together proposal for a trial to compare 4 groups
  - 1.1GBq using T4 withdrawl
  - 1.1GBq using rTSH
  - 3.7GBq using T4 withdrawl
  - 3.7GBq using rTSH
  - Power calculation needed 109-110 patients per group

Results days in hospital



Results

Table 2. **Ablation Success Rates at 6 to 9 Months, According to Four Comparisons of Radioiodine Doses and Methods of Preparation.***

Variable	Comparison 1		Comparison 2	
	Low-Dose Radioiodine	High-Dose Radioiodine	Thyrotropin Alfa	Thyroid Hormone Withdrawal
Ablation success based on diagnostic scan alone — no./total no. (%)	198/214 (92.5)	197/207 (95.2)	197/210 (93.8)	198/211 (93.8)
Risk difference (95% CI) — percentage points	−2.7 (−7.2 to 1.9)		−0.03 (−4.6 to 4.6)	
P value	0.26		0.99	
Ablation success based on thyroglobulin alone — no./total no. (%)	159/186 (85.5)	153/173 (88.4)	162/185 (87.6)	150/174 (86.2)
Risk difference (95% CI) — percentage points	−2.9 (−9.9 to 4.0)		1.4 (−5.6 to 8.3)	
P value	0.41		0.70	
Ablation success based on both diagnostic scan and thyroglobulin — no./total no. (%)	182/214 (85.0)	184/207 (88.9)	183/210 (87.1)	183/211 (86.7)
Risk difference (95% CI) — percentage points†	−3.8 (−10.2 to 2.6)		0.4 (−6.0 to 6.8)	
P value	0.24		0.90	
Risk difference on sensitivity analyses‡	−4.9 (−11.2 to 1.4)		0.4 (−6.0 to 6.8)	

So what now

- Results confirmed by similar French and Taiwanese trails
- Now in UK using 1.1GBq I-131 ablation for low risk patients
- However, as stated the results may be very dependent on the surgeon used. In France and UK very centralised
- However, does show a phase III trial can be done by everyone and save money

Conclusion

- Well run RCT can provide useful answers
- Can be run by companies
- Also can be run by groups of Doctors
- Can result in changes to practice that can help patients
- Respected by other doctors