EVOLUTION AND REVOLUTION IN CANCER CARE

REFLECTIONS ON 30 YEARS OF CLINICAL RESEARCH

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CARDIFF UNIVERSITY

PRIFYSGOL CAERDYDD

DOING RESEARCH WITH IMPACT….

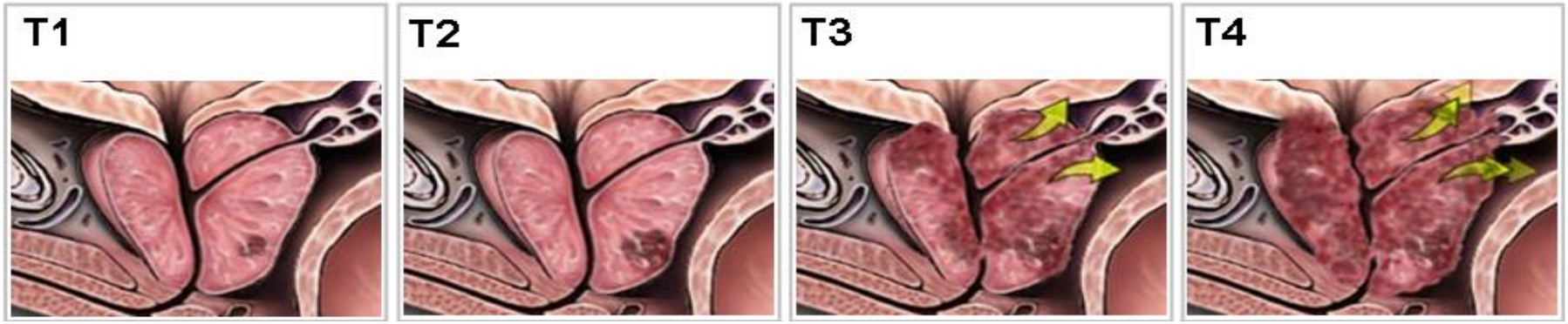
- Only one rule…….

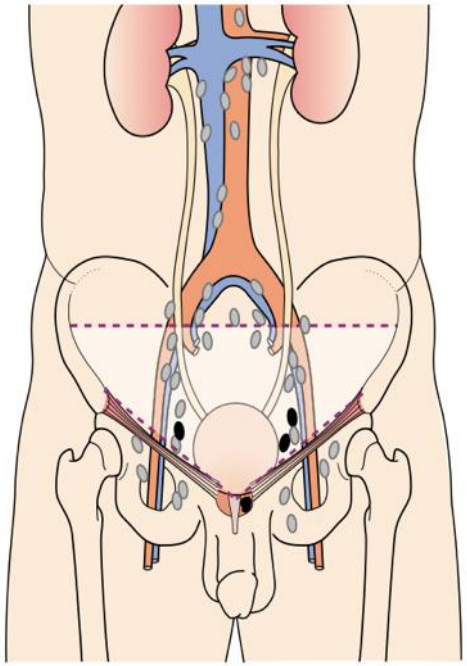
DOING RESEARCH WITH IMPACT….

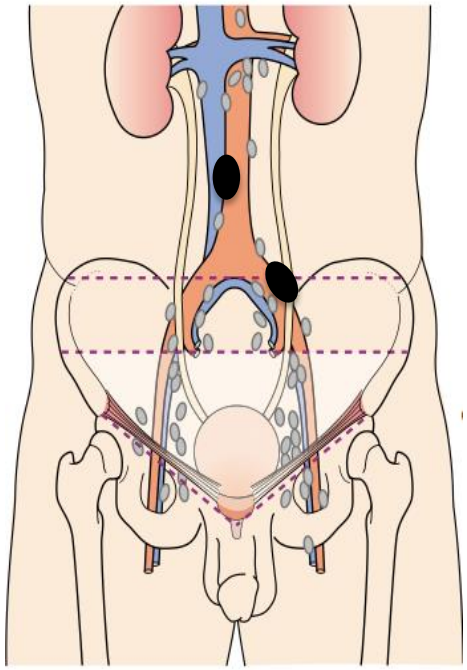
- ASK AN IMPORTANT QUESTION!

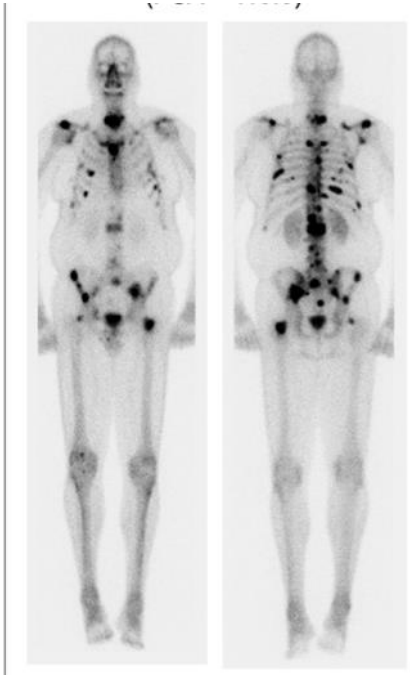
"IMPORTANT" IS NOT THE SAME AS "INTERESTING"…....

- Almost anything that is interesting might be *potentially* important
- Impact depends on the immediacy (actionability) of the importance
- Will it immediately change medical practice?


T1
T2
T3
T4







PROSTATE CANCER: 1986-1990

- Almost no level I evidence!!
- Mortality rates around 12,000 pa in UK

- Is treatment necessary for those in whom it is possible?
- Is treatment possible for those in whom it is necessary?

FOR THOSE IN WHOM IT IS POSSIBLE….

- "Latent" prostate cancer; up to 80% of men have it by the age of 80!
- A disease of the elderly (as viewed in 1990)
- Outcomes after "watchful waiting"

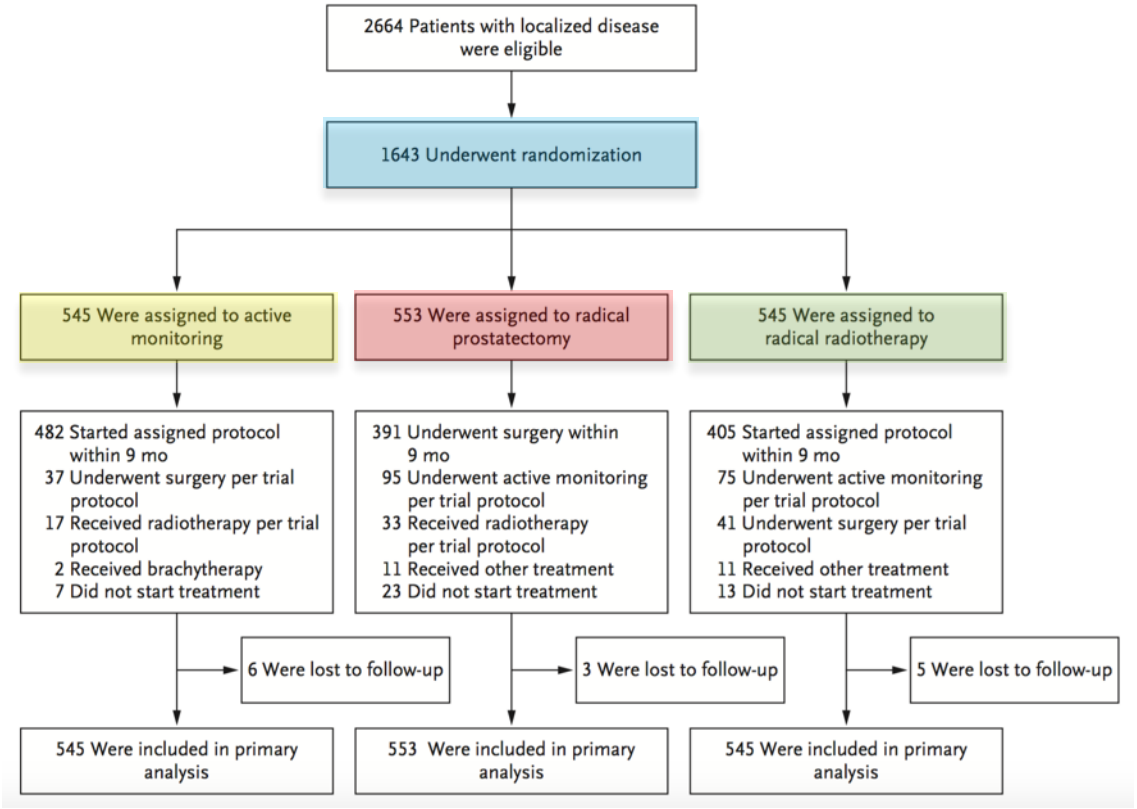
- Do we cure anyone, with M0 disease, or do we just treat those who don't need it?

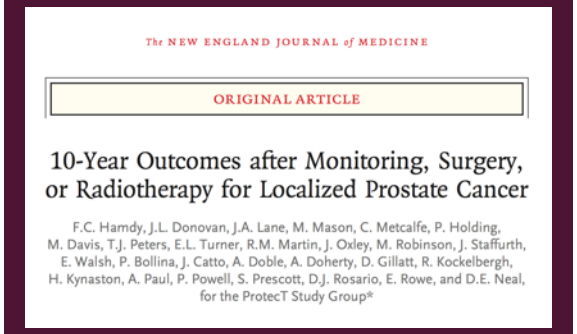
- Surgery?
- Radiotherapy?
- Monitoring?

PROSTATE CANCER AND THE JOHN WEST EFFECT

Only randomised comparisons are valid!

LOCALISED (T1-T2) PROSTATE CANCER DETECTED BY PSA

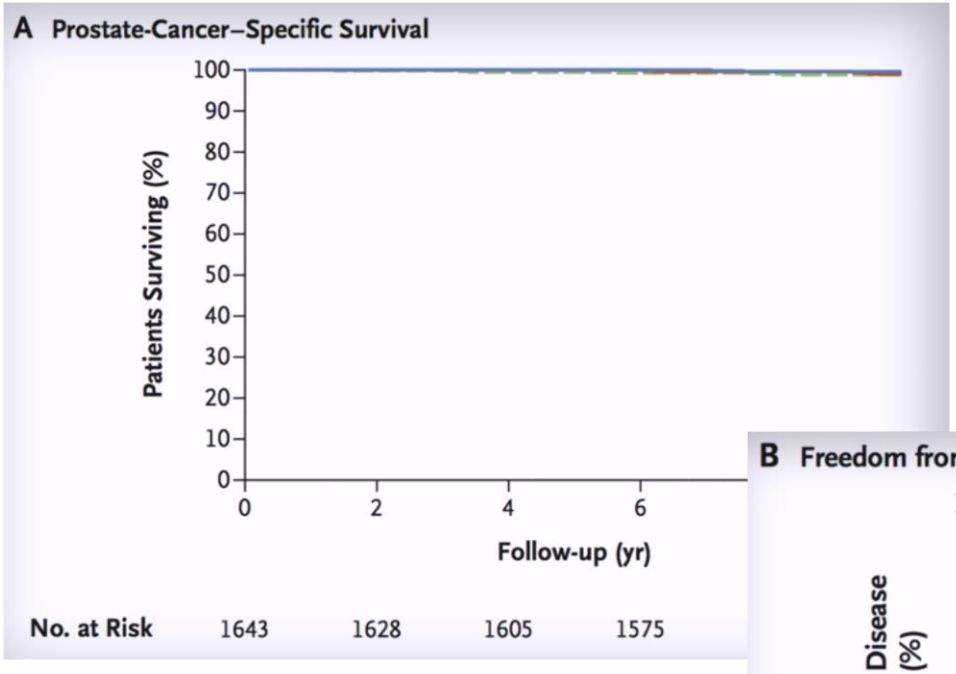


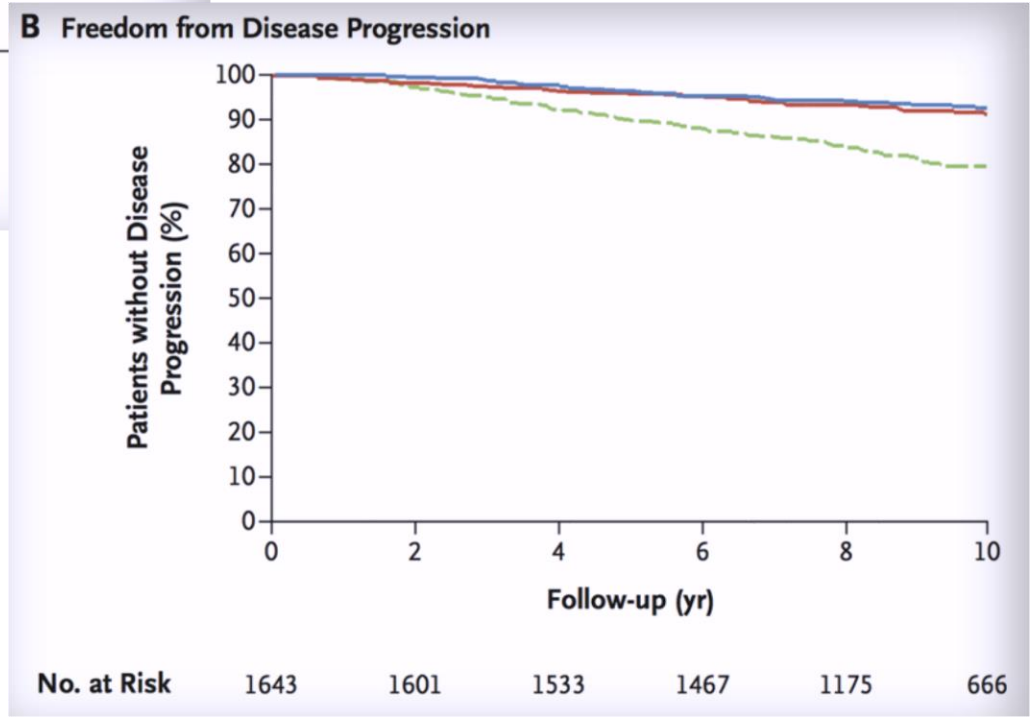

The NEW ENGLAND JOURNAL of MEDICINE

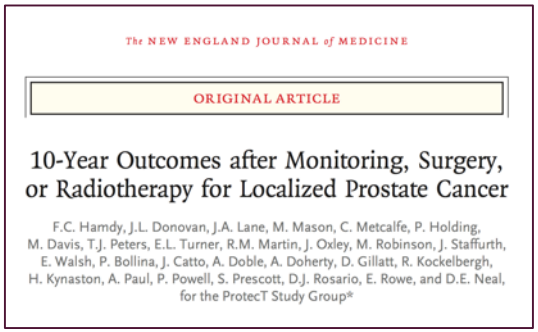
ORIGINAL ARTICLE

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*


A Prostate-Cancer–Specific Survival
Patients Surviving (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
Follow-up (yr)
No. at Risk
1643
1628
1605
1575


B Freedom from Disease Progression
Patients without Disease Progression (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
Follow-up (yr)
No. at Risk
1643
1601
1533
1467
1175
666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…FOR THOSE IN WHOM IT IS NECESSARY….

LOCALLY ADVANCED PROSTATE CANCER 1990: NIHILISM OR OPTIMISM?

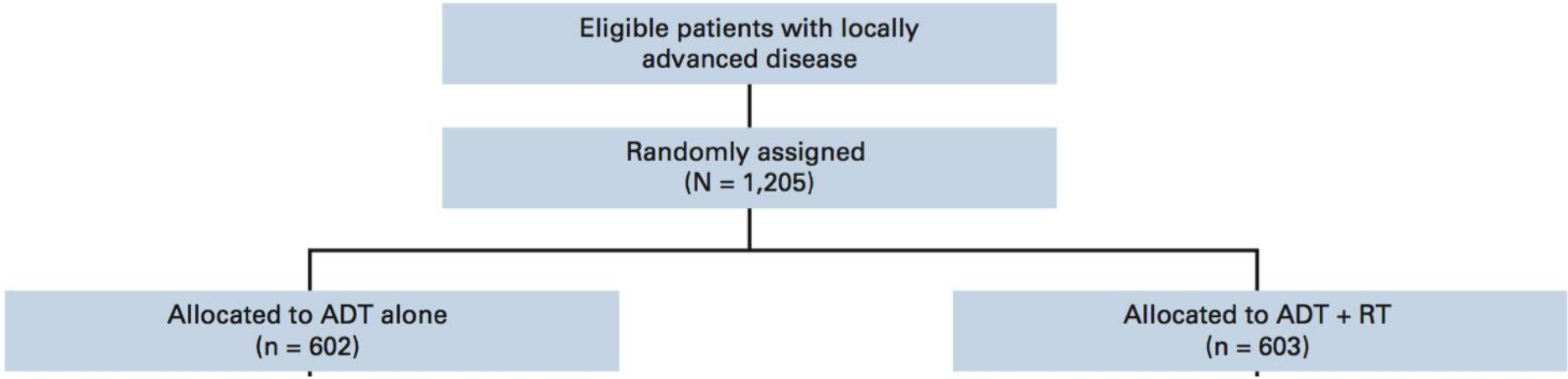
- Hormone therapy: PALLIATIVE
- Radiotherapy: CURATIVE
- MRC Survey 1995:"….these men all have occult micro-metastatic disease. Giving them radiotherapy is meddlesome and unkind...."

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer

Malcolm D. Mason, Wendy R. Parulekar, Matthew R. Sydes, Michael Brundage, Peter Kirkbride, Mary Gospodarowicz, Richard Cowan, Edmund C. Kostashuk, John Anderson, Gregory Swanson, Mahesh K.B. Parmar, Charles Hayter, Gordana Jovic, Andrea Hiltz, John Hetherington, Jinka Sathya, James B.P. Barber, Michael McKenzie, Salah El-Sharkawi, Luis Souhami, P.D. John Hardman, Bingshu E. Chen, and Padraig Warde



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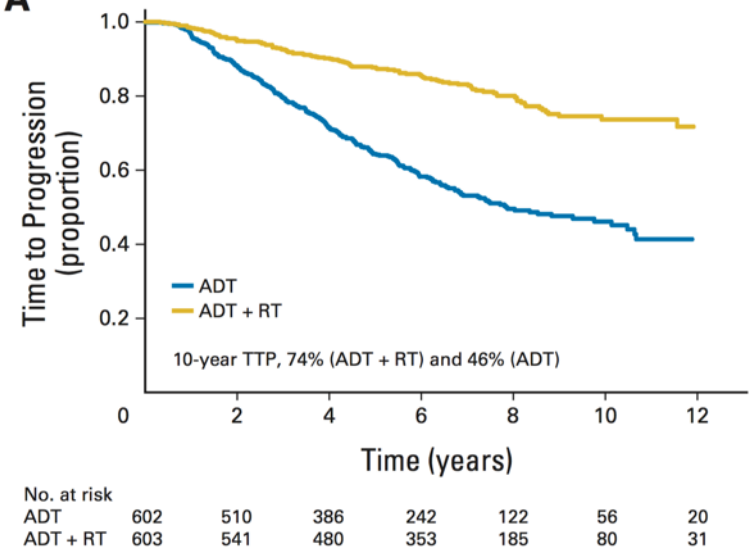
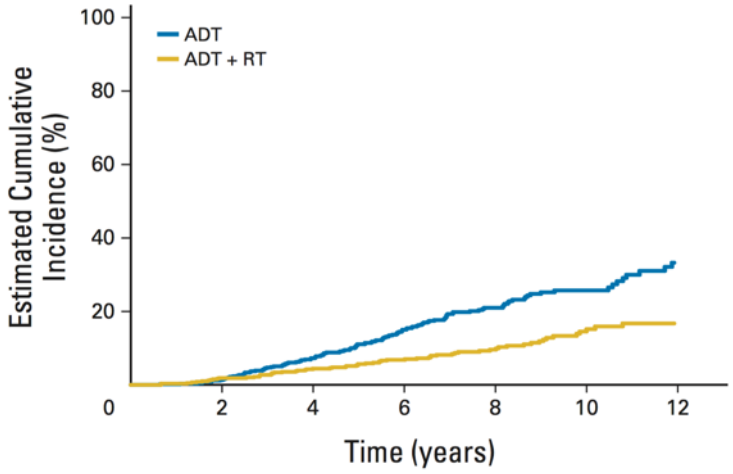
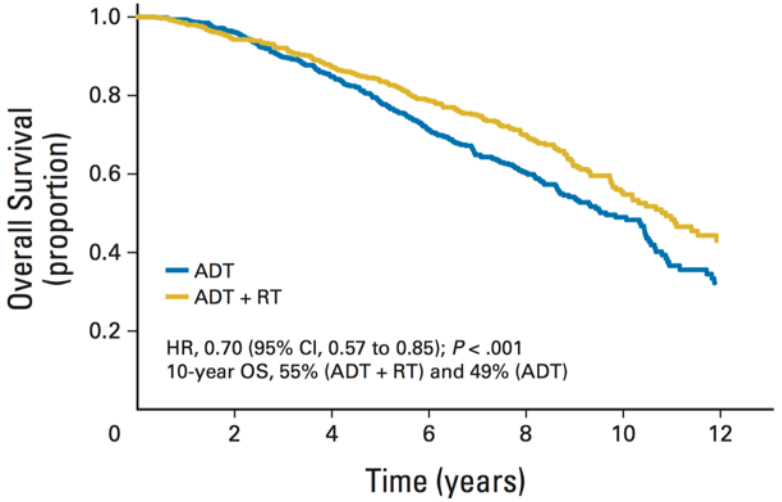


No. at risk

ADT	602	510	386	242	122	56	20
ADT + RT	603	541	480	353	185	80	31





No. at risk

ADT	602	571	498	353	185	77	28
ADT + RT	603	558	505	381	208	85	32

THE BOTTOM LINE: NON-METASTATIC DISEASE

- Treatment IS possible for some men who need it
  - Those with locally advanced disease
  - Combined radiotherapy and hormone therapy
- Treatment MAY NOT BE necessary for most men with PSA-detected localised disease
  - Active monitoring may result in more disease progression
  - 15 and 20 year follow up is needed

ADVANCED AND METASTATIC PROSTATE CANCER - 1941

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 10, 1941)

Carcinoma of the prostate gland is peculiarly favorable for endocrine investigation since frequent serial observations of the activity of phosphatases in serum were found to provide objective indices of activity of the neoplasm when the enzymes were increased in amount above normal. In the present paper data are given for the values of serum phosphatases in carcinoma of the prostate and in normal men. We shall demonstrate that the acid phosphatase of serum is reduced in metastatic carcinoma of the prostate by decreasing the activity of androgens through castration or estrogenic injections and that this enzyme is increased by injecting androgens. We have been unable to find previous observations indicating any relationship of hormones to carcinoma of the prostate gland.

An enzyme capable of hydrolyzing phosphoric esters was discovered by Gessner and Hueter (2) in intestinal mucosa and kidney. Robison (16) found that this enzyme was particularly high in activity in growing bone and cartilage and that its activity was greatest at pH 9 to 9.5. This "alkaline phosphatase" was found by Kay (9) to be increased in the serum in certain bone diseases including metastases of neoplasms to bone and later work has shown that among these conditions is carcinoma of the prostate.

Divers (3) and Barnett and Riedel (1) discovered that there occurs in the spleen and kidney of swine and cattle, in addition to the alkaline phosphatase, a phosphatase with an activity maximum at pH 4.8. An enzyme believed to be identical with this "acid phosphatase" was found by Kutscher and Wolbergs (12) to be present in very large amount in the human prostate gland. This finding of great activity of acid phosphatase in the prostate gland was confirmed and extended to include prostatic cancer by Gutman, Sproul, and Gutman (7). The serum of certain patients with disseminated prostatic carcinoma was found by Gutman and Gutman (6) and Bertrand and Weisland (2) to exhibit increased acid phosphatase activity. Robinson, Gutman, and Gutman (15) summarized the acid phosphatase activity levels of 44 patients with carcinoma of the prostate. They concluded that a marked rise in acid phosphatase in serum is associated with the appearance or spread of roentgenologically demonstrable skeletal metastases and implies dissemination of the primary tumor and thus is of unfavorable prognostic significance.

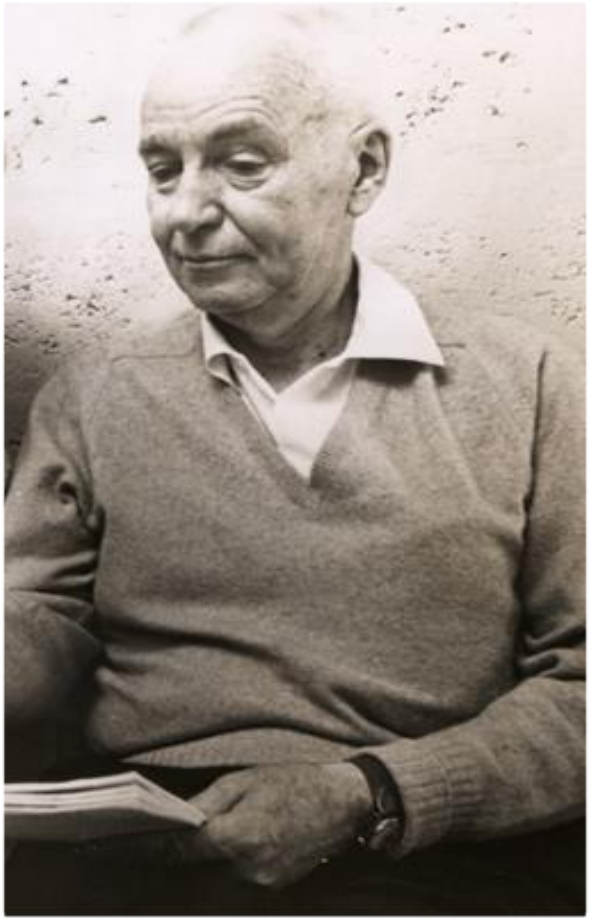
* This investigation was aided by a grant from the Committee on Research in Problems of Sex, the National Research Council.

Methods and Materials

The phosphatase activity of serum was determined by the method of King and Armstrong (10) using 0.005 M disodium monophenylphosphate as substrate. The buffers used were 0.05 M barbital-sodium at pH 9.3, and 0.1 M Sörensen's citrate-HCl or Walpole's 0.2 N sodium acetate-acetic acid buffers at pH 5. All serums were tested in duplicate and were added directly to buffer-substrate solutions without dilution; they were incubated at 37.5° C. for 30 minutes. Precautions were observed that all solutions were at this temperature before testing. Blanks were run by adding the protein precipitant to the buffer-substrate solution before adding serum. Colorimetric procedures were carried out with the Evelyn photoelectric colorimeter using a 6600 Å filter. The results are expressed in King and Armstrong units, a unit being defined as that degree of phosphatase activity which at pH 9.3 (or pH 5.0, respectively) and 37.5° C. will liberate 1 mgm. of phenol from the specified buffer-substrate solution in one-half hour.

Phosphatase determinations at pH 5 and 9.3 were made on the serum of 40 normal men, of 21 men with benign prostatic hypertrophy, and of 47 men with carcinoma of the prostate. The diagnosis of carcinoma of the prostate gland was derived from one or more of the following procedures: rectal palpation, cystoscopic examination, transurethral resection with microscopic examination, or roentgenologic evidence of skeletal metastases. Necropsy was obtained in 2 cases. All patients had x-ray studies of the bony pelvis.

Eight patients who had carcinoma of the prostate with skeletal metastases and with moderate or great elevation of acid phosphatase of serum values above 20 units in 100 cc. were selected for intensive study in the hospital. Each patient also had elevation of alkaline phosphatase in the serum. Both of these enzymes were determined on the serum 3 times weekly for many weeks. Bilateral castration was carried out in all. Five patients were injected with stilbestrol, 1 mgm.



STAMPEDE AND THE MAMS REVOLUTION

Patients eligible for STAMPEDE

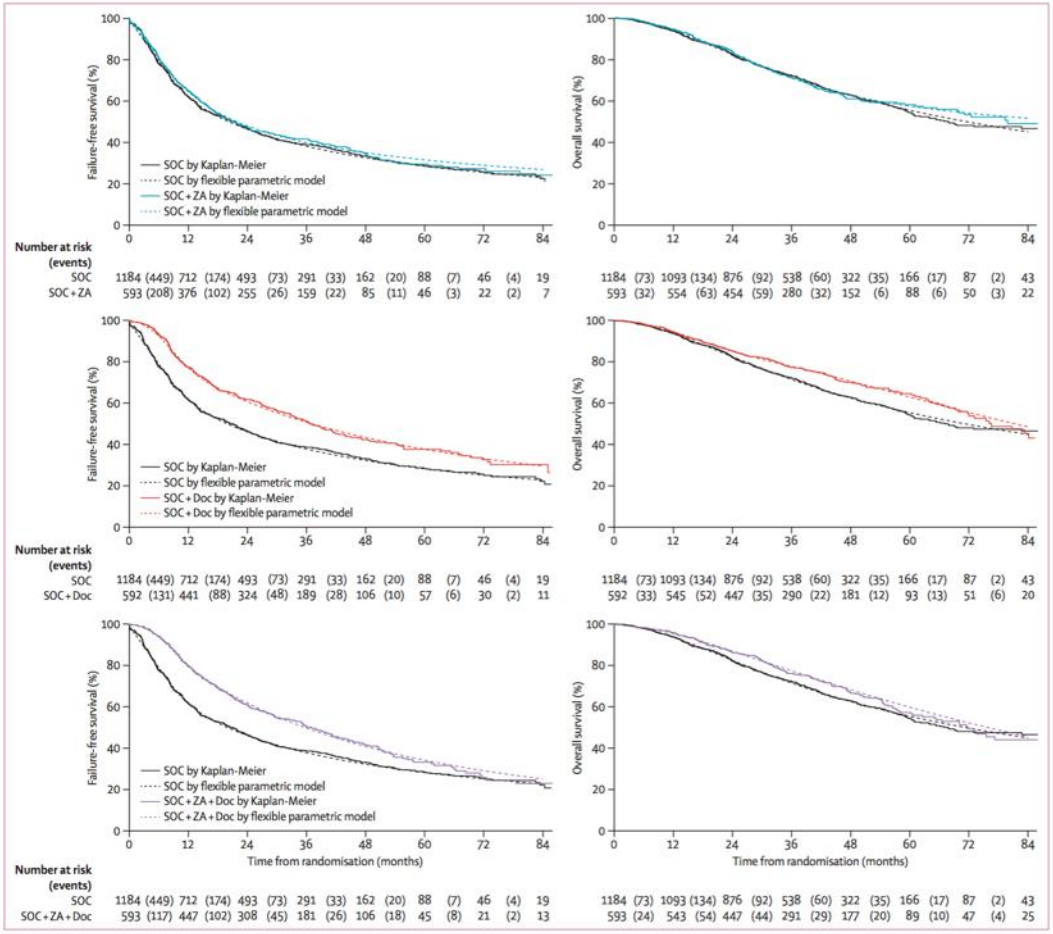
↓

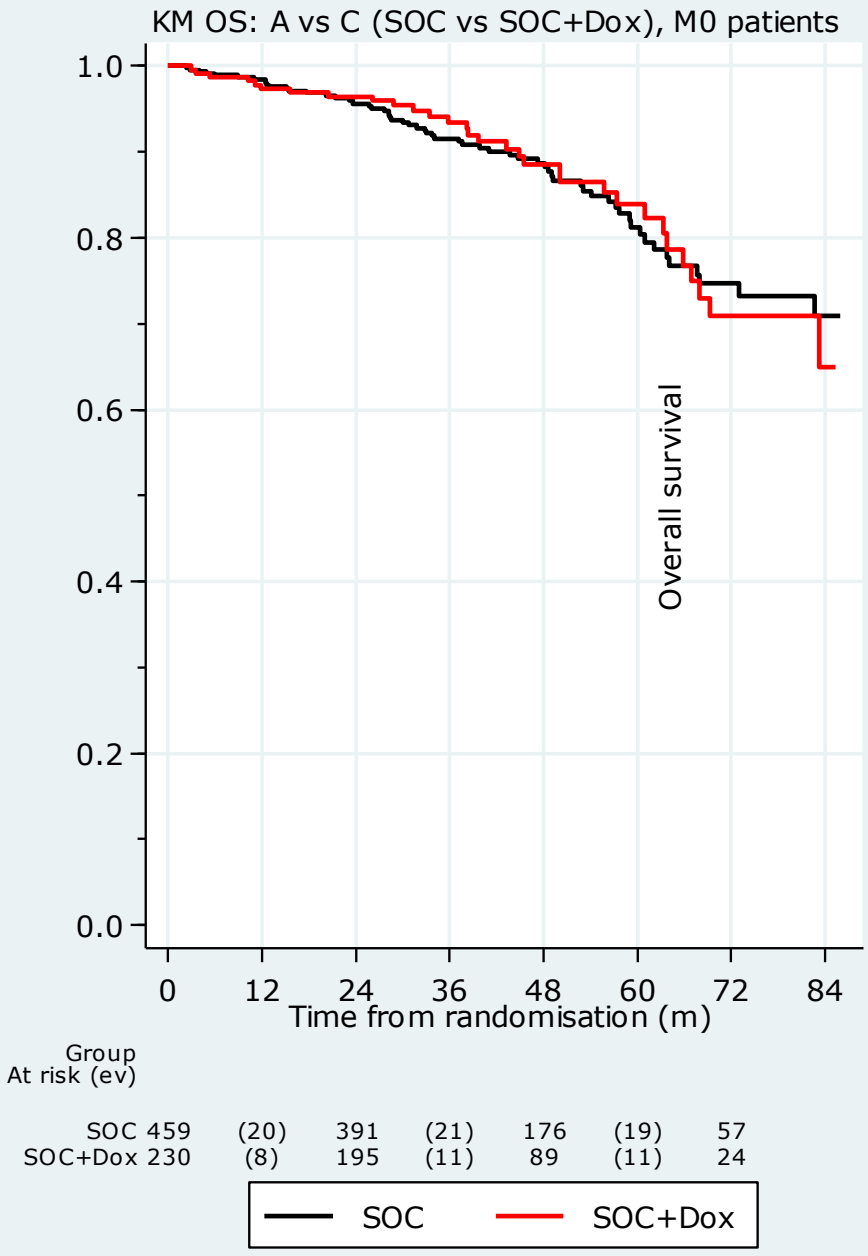
STARTING LONG-TERM HORMONES

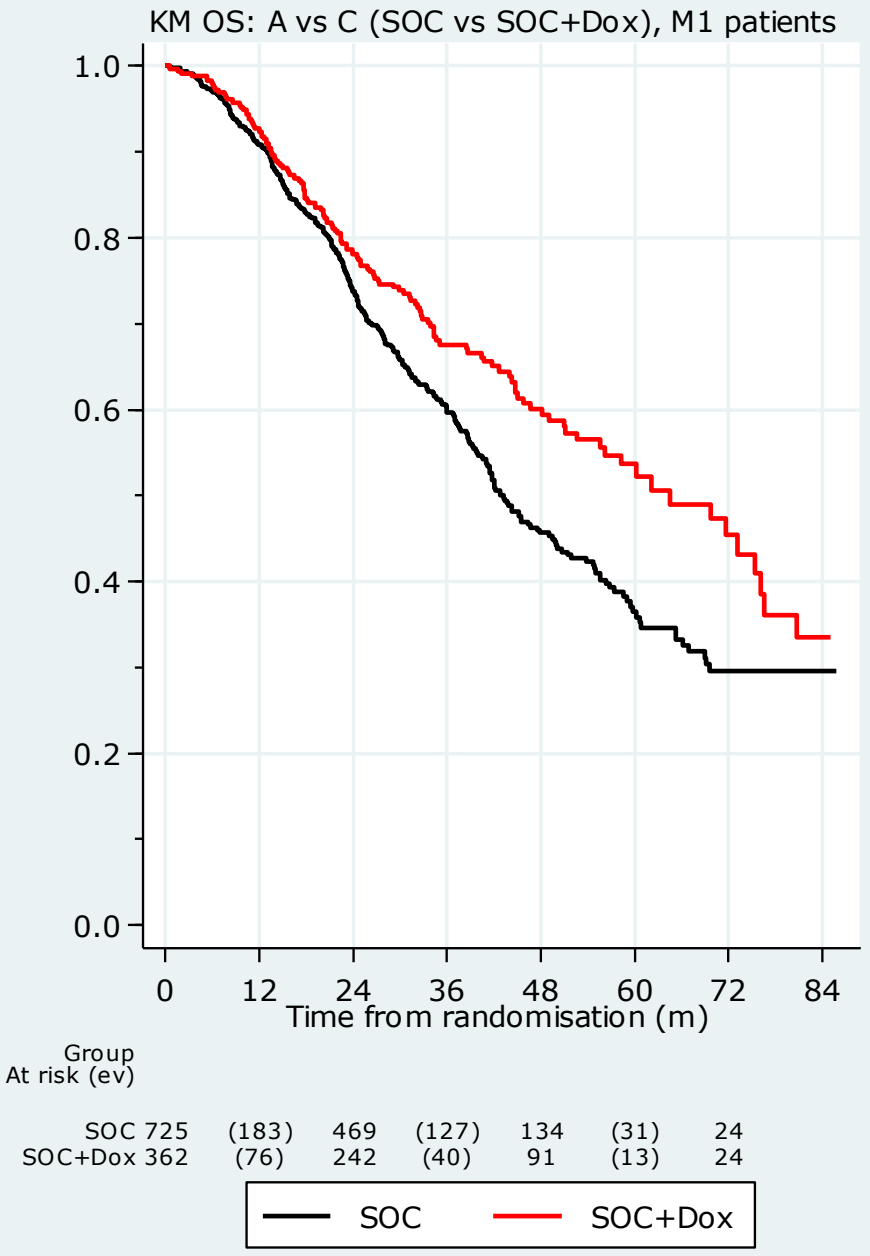
RANDOMISATION	
A	ADT
B	ADT + zoledronic acid
C	ADT + docetaxel
D	ADT + celecoxib
E	ADT + ZA + docetaxel
F	ADT + ZA + celecoxib

MRC | Clinical Trials Unit

STAMPEDE – FIRST OUTCOMES, 2015



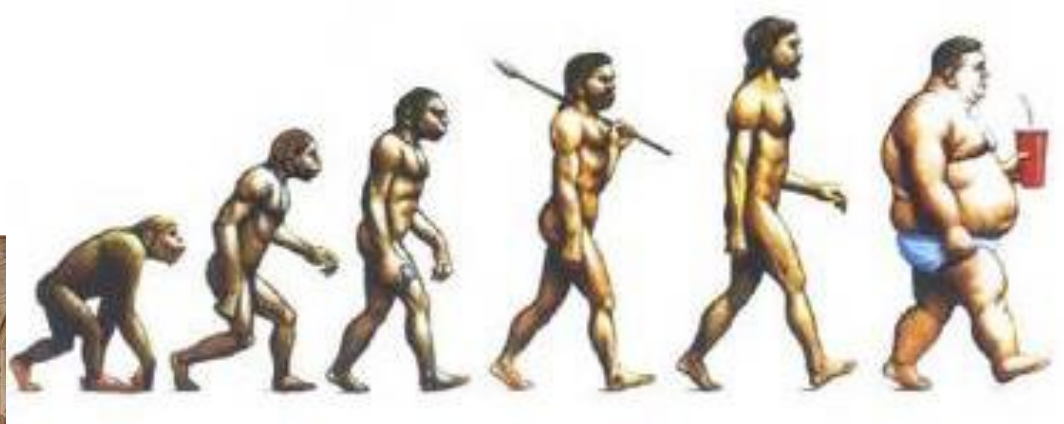

KM OS: A vs C (SOC vs SOC+Dox), M0 patients
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
0
12
24
36
48
60
72
84
Time from randomisation (m)
Group
At risk (ev)
SOC 459 (20) 391 (21) 176 (19) 57
SOC+Dox 230 (8) 195 (11) 89 (11) 24
SOC
SOC+Dox


KM OS: A vs C (SOC vs SOC+Dox), M1 patients
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
Time from randomisation (m)
Group
At risk (ev)
SOC 725 (183) 469 (127) 134 (31) 24
SOC+Dox 362 (76) 242 (40) 91 (13) 24
SOC
SOC+Dox

THE BOTTOM LINE: METASTATIC DISEASE

- Chemotherapy with docetaxel improves overall survival and failure-free survival, added to ADT in men with metastatic disease
- As yet, it does not improve survival in M0 patients, but it does delay treatment failure

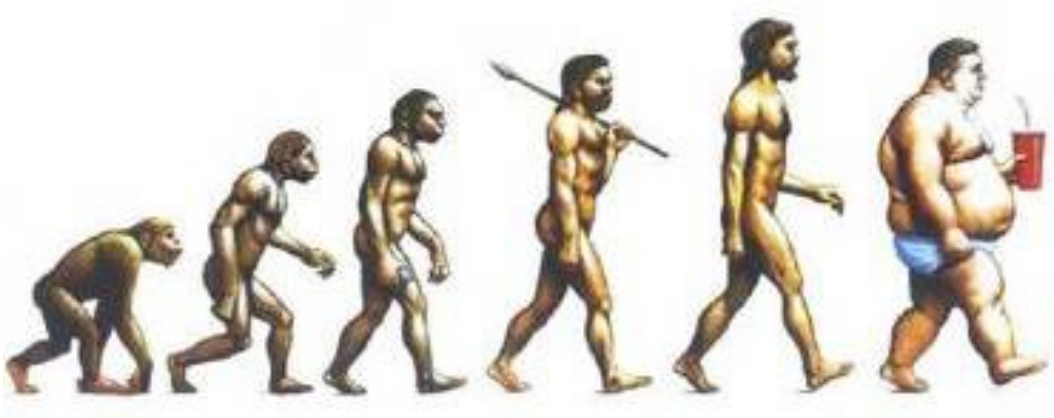
EVOLUTION OR REVOLUTION?



EVOLUTION OR REVOLUTION?

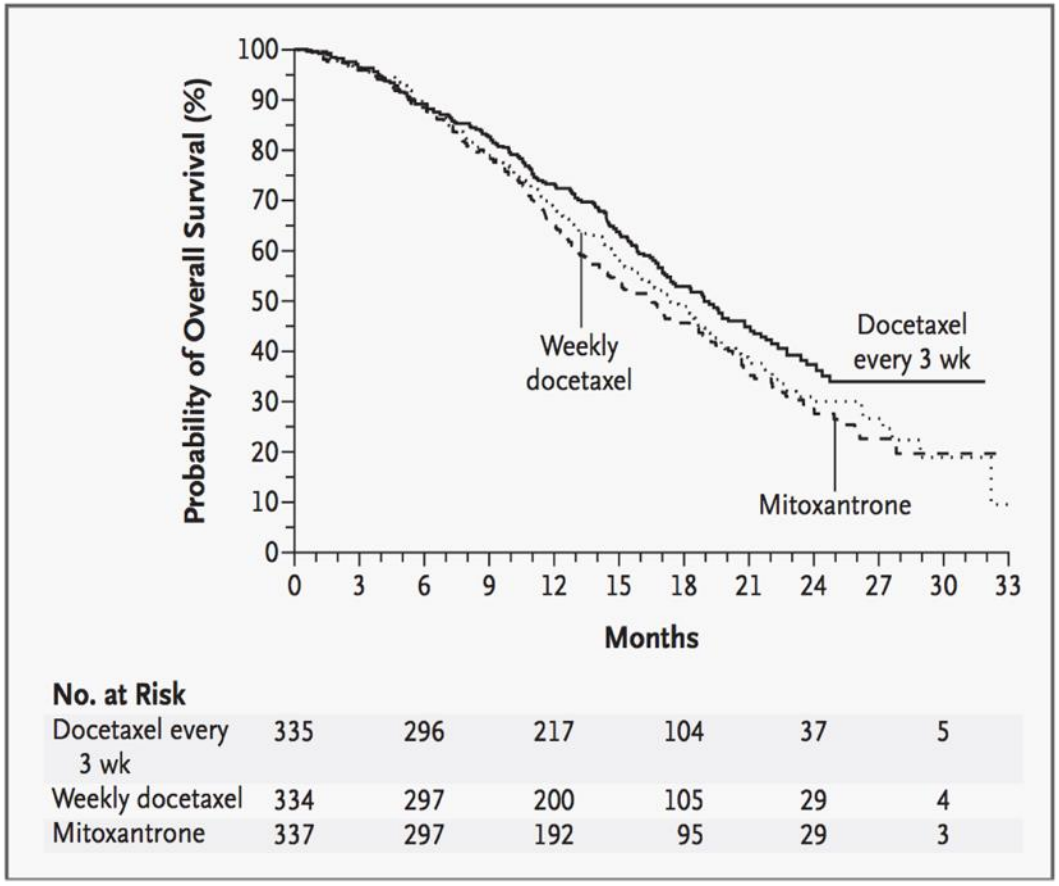
- Where the technology is already being used, and the efficacy is great enough…
- Worldwide change in medical practice, enshrined in international treatment guidelines

EVOLUTION OR REVOLUTION?



- Usually, treatment benefits are modest, such that a randomised trial is needed
- Smaller changes in efficacy can still trigger a change in practice
- Modest benefits in advanced disease might translate into large benefits in early disease (docetaxel in M0 prostate cancer???.....)

DOCETAXEL IN CASTRATE REFRACTORY PROSTATE CANCER - 2004



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

DRUGS WHICH PROLONG SURVIVAL IN ADVANCED, CASTRATE-REFRACTORY PROSTATE CANCER

- Docetaxel
- Cabazitaxel
- Abiraterone
- Enzalutamide
- Sipuleucel-T
- Alpharadin

DRUGS WHICH PROLONG SURVIVAL IN ADVANCED, CASTRATE-REFRACTORY PROSTATE CANCER

- Docetaxel
- Cabazitaxel
- Abiraterone
- Enzalutamide
- Sipuleucel-T
- Alpharadin

MRC Clinical Trials Unit

EUROPEAN UROLOGY FOCUS XXX (2015) XXX–XXX

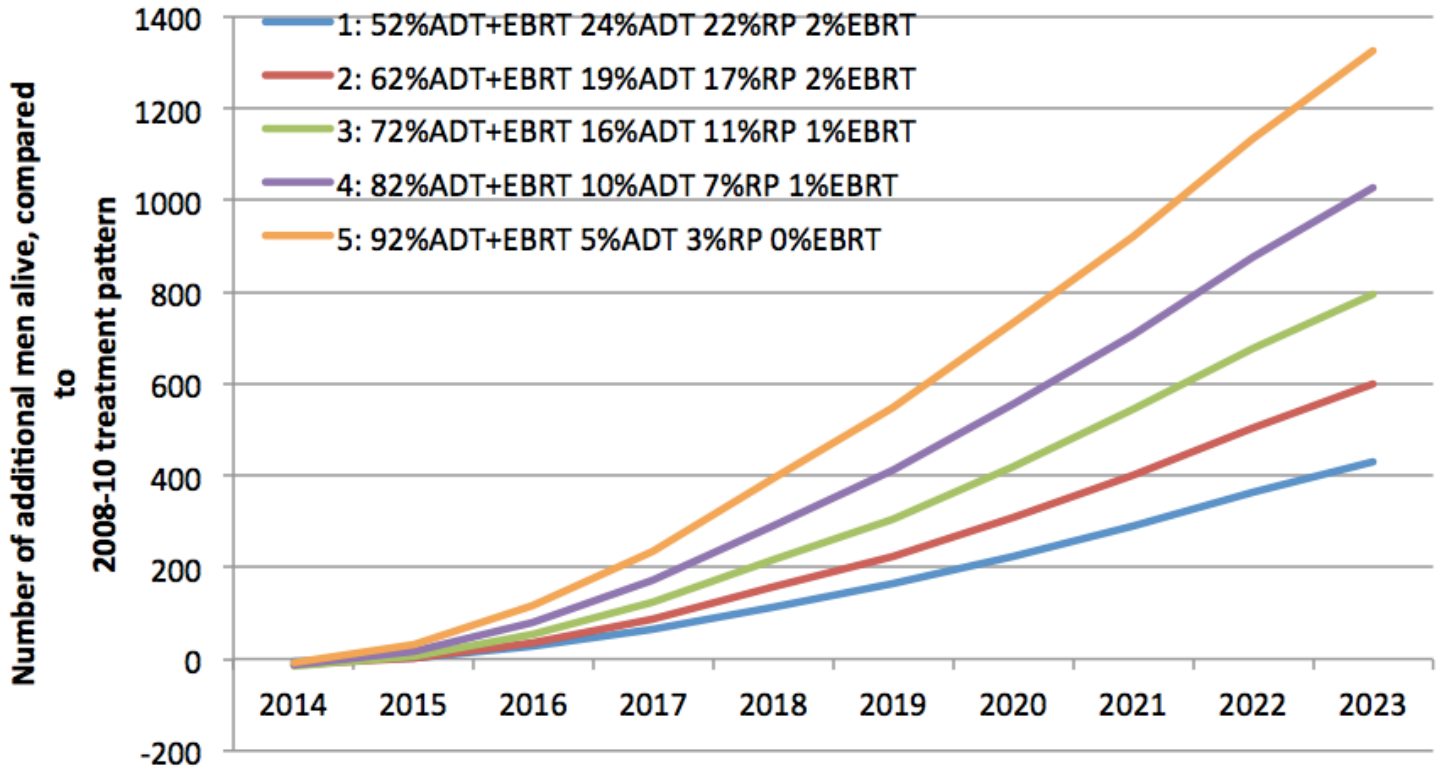
available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus

Prostate Cancer

Estimating the Impact of Randomised Control Trial Results on Clinical Practice: Results from a Survey and Modelling Study of Androgen Deprivation Therapy plus Radiotherapy for Locally Advanced Prostate Cancer

Annabelle South[a,*], *Wendy R. Parulekar*[b], *Matthew R. Sydes*[a], *Bingshu E. Chen*[b], *Mahesh K. Parmar*[a], *Noel Clarke*[c], *Padraig Warde*[d], *Malcolm Mason*[e]

[a] Medical Research Council Clinical Trials Unit, University College London, London, UK; [b] NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada; oronto, ON, Canada; [e] Cardiff University School



THE FUTURE: STRATIFIED (PRECISION) MEDICINE

- Not every patient benefits from treatment….
- Some patients might benefit enormously.....

THE STAMPEDE BIOREPOSITORY




COLLECT up to 7,000 tissue blocks (retrospective) and 2,000 blocks (prospective)

Underpin key translational questions

Pathology and tissue processing facilities

MRC Medical Research Council

CANCER RESEARCH UK