Aims/Plan

Set the scene; use MEGS slides from ICPC

Define high risk: various definitions, PSA kinetics, molecular markers, interpretation of biopsy tumour volume, biopsy PN invasion

Say that HR outcomes are poor: compare RT versus surgery

Discuss stage migration

Present current surgical outcomes

- Largest series
- Our series- both salvage and HR alone

Technical issues

Present data on adjuvant and neoadjuvant therapy:

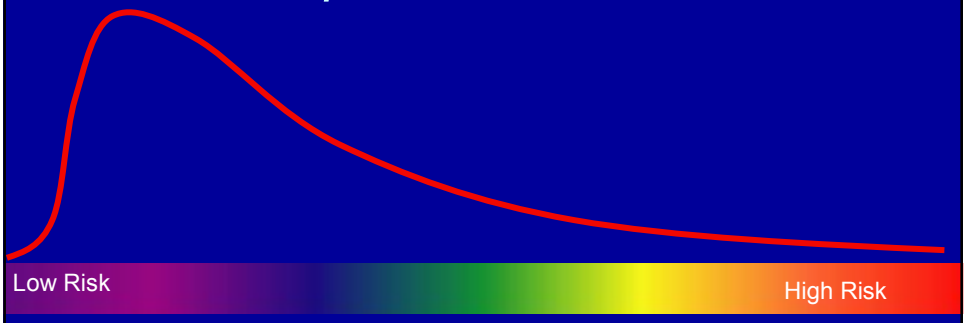
- Chemotherapy

Present data on new approaches.

Surgical Management of High Risk Prostate Cancer

Rod Studd
Uro-Oncology Fellow

Prostate Cancer, *a spectrum of disease*



NNT: 50-100

Many men die of their disease despite treatment…

Current treatment paradigm….

Surrogate PSA screening

Identification of a large number of *low risk* cases

And a smaller number of *high risk* cases

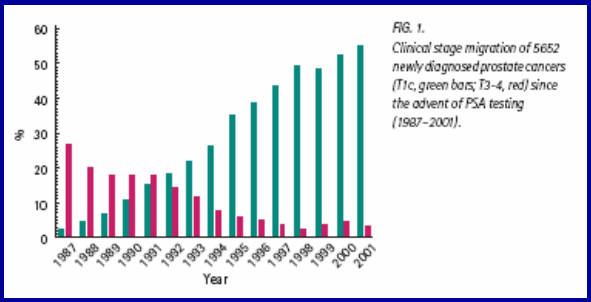


FIG. 1.
Clinical stage migration of 5652 newly diagnosed prostate cancers (T1c, green bars; T3–4, red) since the advent of PSA testing (1987–2001).

Ward et al, BJU Int 2005

Current treatment paradigm….

Surrogate PSA screening

Identification of a large number of *low risk* cases

And a smaller number of *high risk* cases

Most get treated

Current treatment paradigm….

Surrogate PSA screening

Identification of a large number of *low risk* cases

And a smaller number of *high risk* cases

Over treatment of many low risk cases

Most get treated

Most do well with Contemporary Rx

Current treatment paradigm….

Surrogate PSA screening

Identification of a large number of *low risk* cases

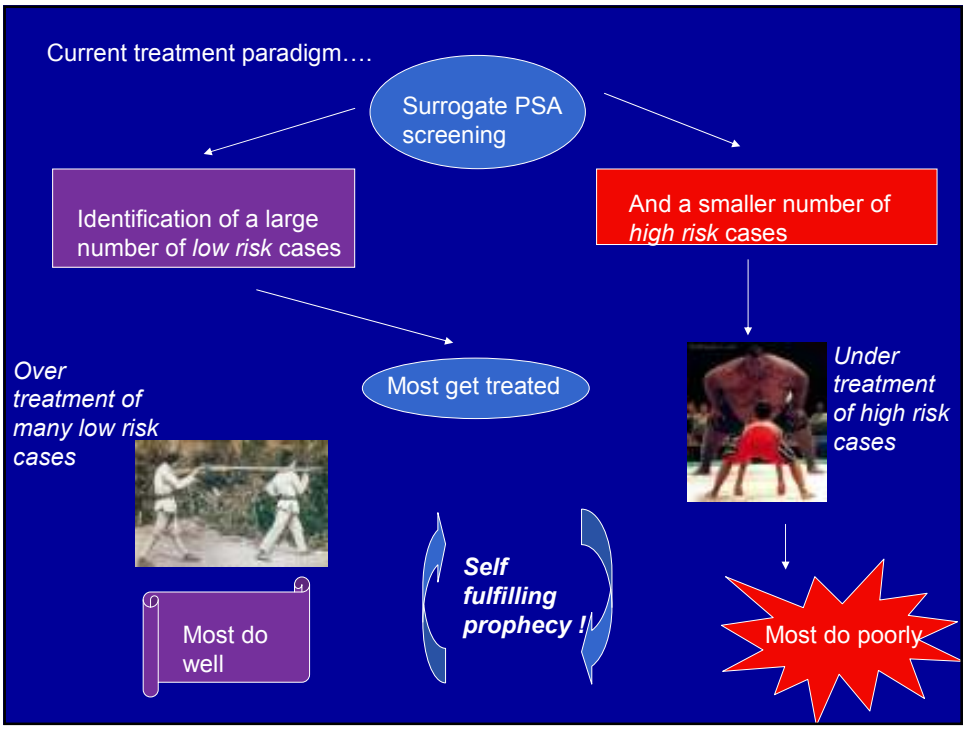
And a smaller number of *high risk* cases

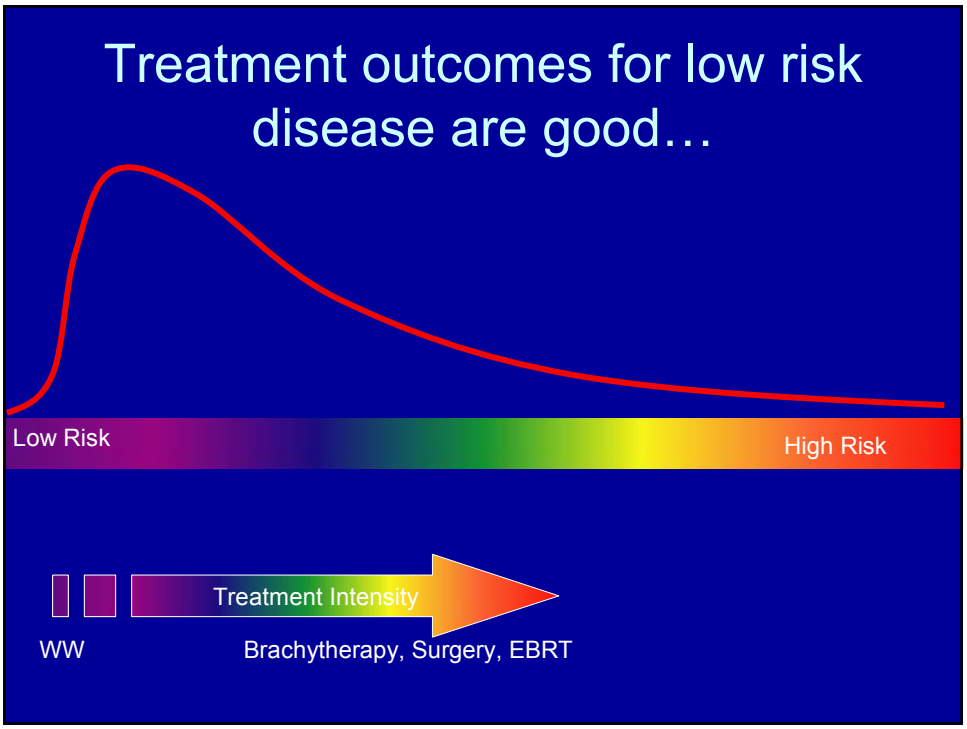
Over treatment of many low risk cases

Most get treated

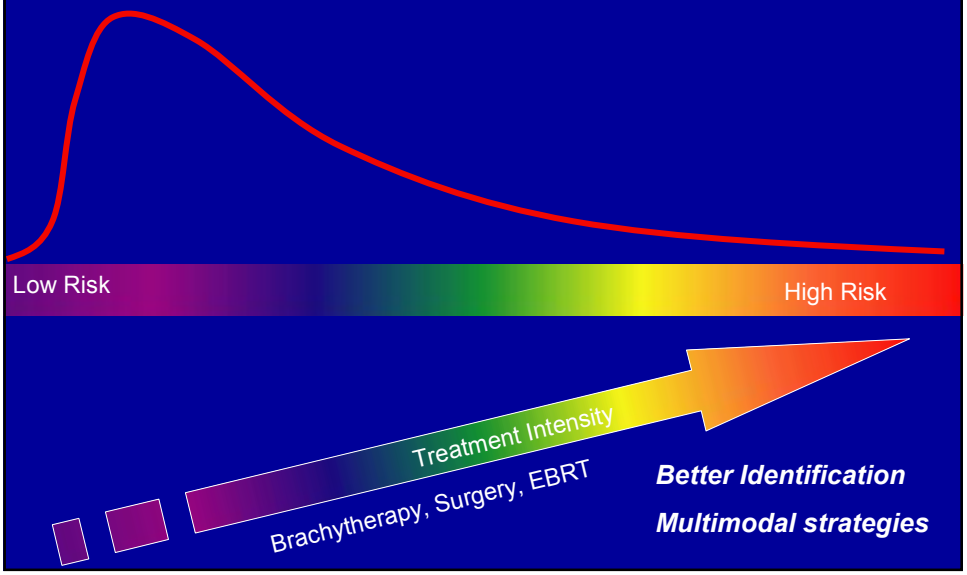
Relative Under treatment of high risk cases

Most do well


Current treatment paradigm….
Surrogate PSA screening
Identification of a large number of *low risk* cases
And a smaller number of *high risk* cases
Over treatment of many low risk cases
Most get treated
Under treatment of high risk cases
Most do well
Self fulfilling prophecy !
Most do poorly


Treatment outcomes for low risk disease are good…
Low Risk
High Risk
Treatment Intensity
WW
Brachytherapy, Surgery, EBRT

But not so good for high risk disease..



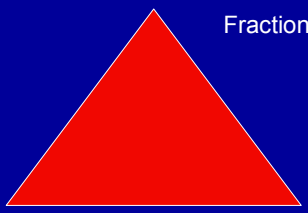
Improving identification of high risk disease

Identification of the HR patient should be based on factors that are significantly associated with PCSM

Biopsy Features

Gleason Score

Fractional Core involvement



DRE

PSA

At diagnosis

PSA kinetics

Future ----***Genetic factors***

Identifying Men at High-risk for Prostate Cancer *Death* Following Surgery or Radiation Therapy

1453 men underwent RT or RP for T1c, T2 disease, Median FU of 4.5 years

Prostate Cancer Specific Mortality:

Pre-Op Variable	Analyzed	p-Value RP	p-Value RT
PSA	continuous	0.001	0.04
Biopsy Gleason score	8 or more vs 7 vs 6 or less	0.024 0.17	<0.0001 0.02
Clinical Stage	T2 vs T1c	<0.0001	0.07

Anthony D'Amico; JNCI: 2003: 95: 1376-83

Identifying Men at High-risk for Prostate Cancer *Death* Following Surgery or Radiation Therapy

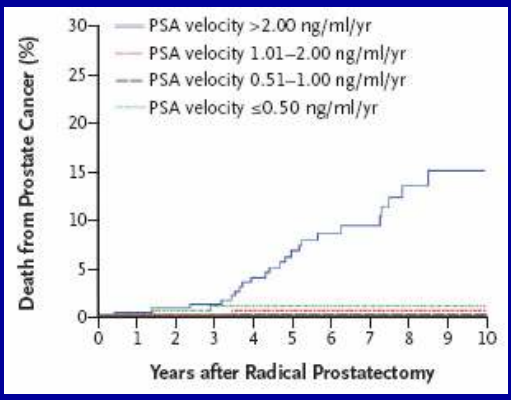
1453 men underwent RT or RP for T1c, T2 disease, Median FU of 4.5 years

Prostate Cancer Specific Mortality:

Pre-Op Variable	Analyzed	p-Value RP	p-Value RT
PSA velocity	>2.0 vs 2.0 or less	<0.001	<0.001
PSA	continuous	0.001	0.04
Biopsy Gleason score	8 or more vs 7 vs 6 or less	0.024 0.17	<0.0001 0.02
T-category	T2 vs T1c	<0.0001	0.07

Anthony D'Amico; JNCI: 2003: 95: 1376-83

PSA Velocity *Predicts P-Stage, Recurrence & Death*



PSA Velocity >2ng/mL significantly associated with:

LN metastases, high stage, high grade, shorter time to recurrence and death

Death rate from CaP of 9.2% within 7 years of RP

Recommend:

- Analyze PSA velocity in otherwise low-risk
- Consider men with PSA-velocity >2ng/ml as ***high risk***
- Therefore NOT candidates for WW and possible candidates for clinical trial of systemic therapy plus RP

DRE- *The least precisely assessed pre-operative determinant of disease risk*

565 men assessed clinically and pathologically by one urologist & pathologist

Partin et al, J Urol, 1993

DRE suggested T2

- 52% pT2
- 48% pT3
  - 31% capsular penetration
  - 17% SVI

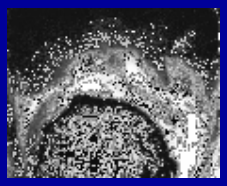
Poor accuracy!

DRE suggested T3

- 19% pT2
- 81% pT3
  - 36 % capsular penetration
  - 45% SVI or LN +

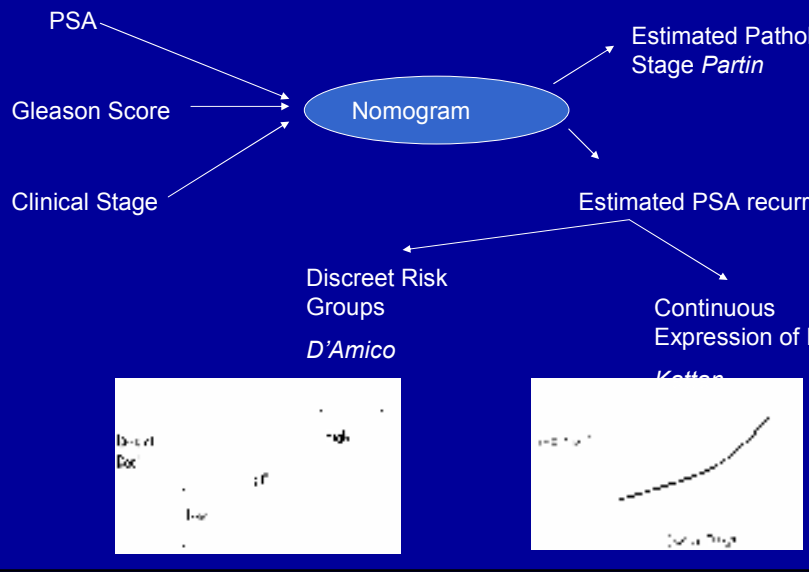
However: Stage migration within high risk group towards high grade T2 lesions

Endorectal MRI – *Improves Staging over DRE*



Not widely available

Nomograms – *Discreet or Continuous Expression of Risk*

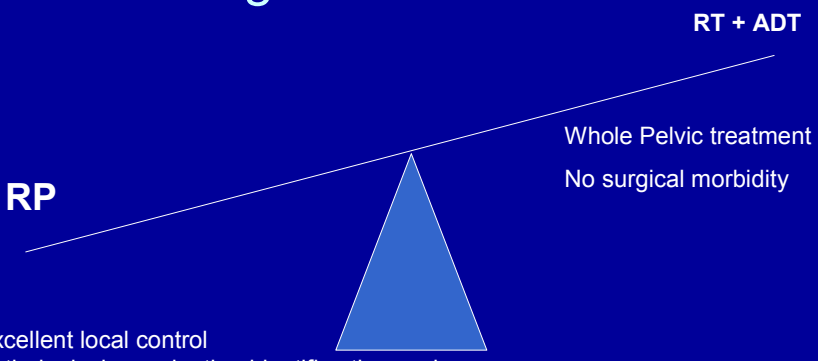


Selecting the Appropriate Local Modality

?RP
?RT
?BT

Adequacy of local treatment affects PSA recurrence rate

Potential Advantages of Surgery for High Risk Disease



- Excellent local control
- Pathological examination identifies those who may benefit from adjuvant RT or ADT
- Interpretation of PSA during follow up is simpler
- Complete prostate removal reduces the likelihood of delayed dissemination of radio-resistant cells
- Reduced toxicity of long term ADT

The Largest High Risk Surgical Series:

Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome

JOHN F. WARD, JEFFREY M. SLEZAK*, MICHAEL L. BLUTE†, ERIK J. BERGSTRALH* and HORST ZINCKE†

*Division of Urology, Naval Medical Center, Portsmouth, VA, *Division of Biostatistics, and †Department of Urology, Mayo Clinic, Rochester, MN, USA*

Accepted for publication 2 December 2004

Series accrued from 1987-1997

841 had RP for T3 disease

Median FU 10.3 years

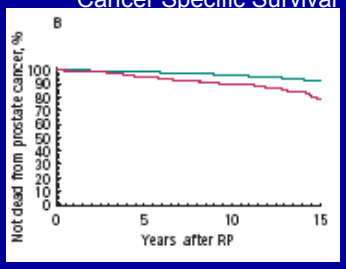
Variable	Median (25–75th percentile) cT2	cT3
N	4810	841
Age at RP, years	66 (61–70)	66 (61–70)
Pre-op PSA, ng/mL	7.2 (4.4–11.9)	10.2 (4.7–23.7)
Clinical grade	6 (5–7)	7 (6–7)
Clinical grade ≥7, %	31	54
Neoadjuvant therapy	5	23

Results

- ***27% were clinically over-staged; therefore monotherapy potentially curative!***
- Positive surgical margins in 56%
- Positive LN in 27%

AT 15 yrs	T3	T2
Freedom from clinical disease	67%	?
Freedom from biochemical disease	38%	52%
Cancer specific survival	79%	92%
Overall survival	53%	61%

Cancer Specific Survival



Several Factors Predicted for Recurrence:

TABLE 5 Multivariate analysis with hazard rates for clinical disease recurrence after RP in patients with cT3 prostate cancer (systemic or local disease)

Variable	Hazard ratio (95% CI)	P
Pathological grade ≥7	1.27 (1.03–1.56)	0.026
Pre-op PSA (doubling)	1.13 (0.96–1.34)	0.154
Ploidy (non-diploid)	1.85 (1.18–2.91)	0.008
Positive surgical margin	1.77 (1.12–2.79)	0.015
Seminal vesicle invasion	1.49 (0.92–2.43)	0.108

Function

Erectile No erectile function in 75%

Wide excision of both NVB's in 74%,

bilateral preservation 12%

unilateral preservation 14%

Continence At one year: *cT3 79% 'continent'*

cT2 84% 'continent'

Complication rate similar between cT2 and cT3

VGH Series

High risk defined as:

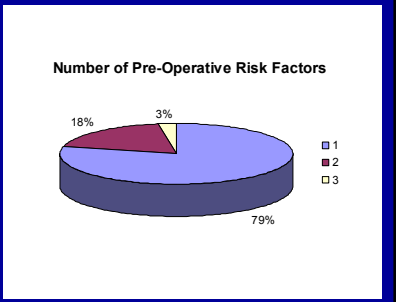
PSA >20 or biopsy Gleason score >7 or clinical stage T3

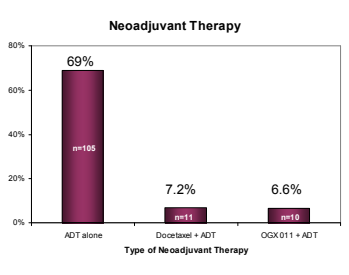
152 men with a median age of 63 years (45.5-75.9)

- 36% PSA >20
- 63% Gleason score >7
- 20% clinical stage T3

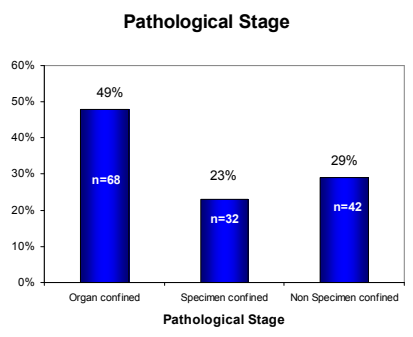
NHT: 83%

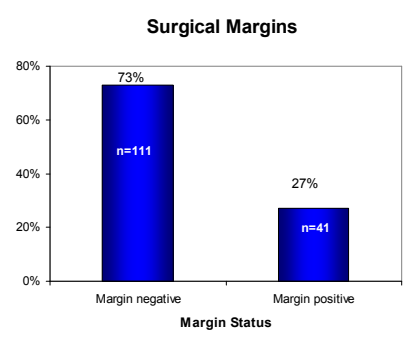
Median follow-up 3.3 yrs





VGH Series- Surgical Pathology

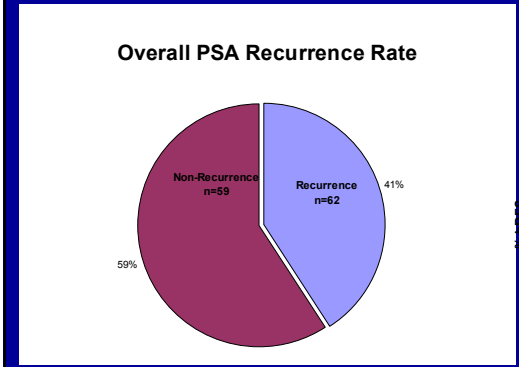


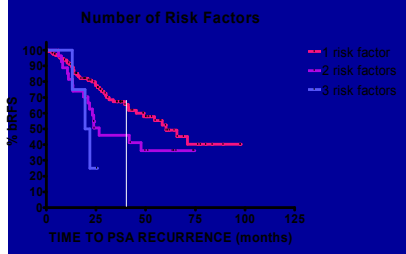


PSA Recurrence

The overall PSA recurrence rate was 41% (62)

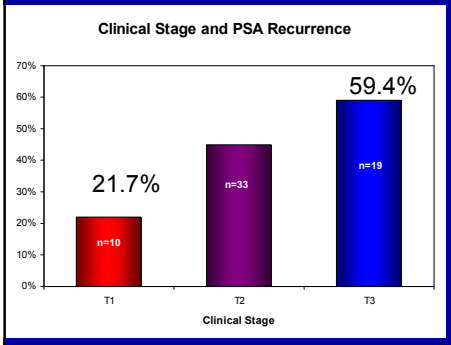
PSA recurrence occurred a median of 21 months post surgery (immediately -9 years).

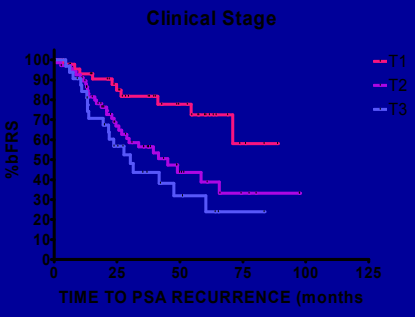




The risk of PSA recurrence increased with clinical stage..

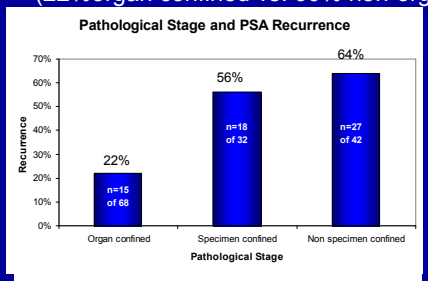
(21.7% T1 vs. 59.4% T3, P=0.008)

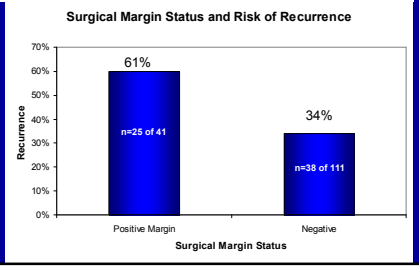


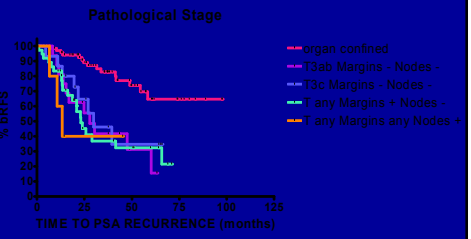


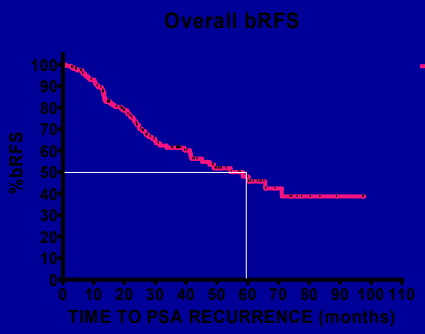
The risk of PSA recurrence increased with pathological stage..

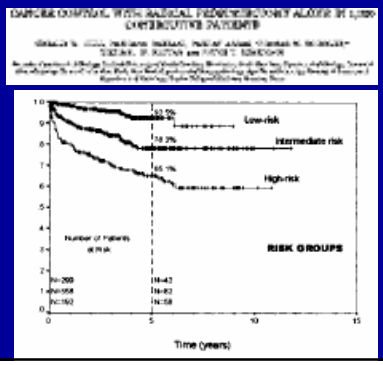
(22%organ confined vs. 60% non-organ confined, P=<.05).











*High risk included T2c

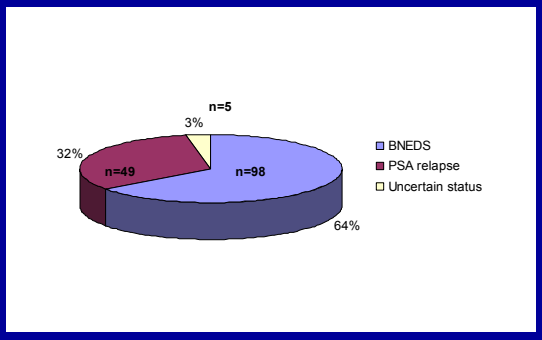
Salvage Radiotherapy

20 patients received salvage RT

6 have had a PSA relapse post RT

5 are unable to be assessed for recurrence due to castrate T levels

Accounting for salvage RT, 64% have no biochemical evidence of disease after median FU of 3.3 years



How can we improve Surgical Outcomes?

Pelvic LN Dissection?

Modification to Surgical Techniques?

Is PLND Therapeutic?

Yes, for some cancers…

Removal of LN metastases influences progression of penile, breast, colon cancers & melanoma

In prostate cancer PLND long considered a staging procedure only

Often omitted in low risk disease

Incidence of Lymph Node Metastasis is Falling

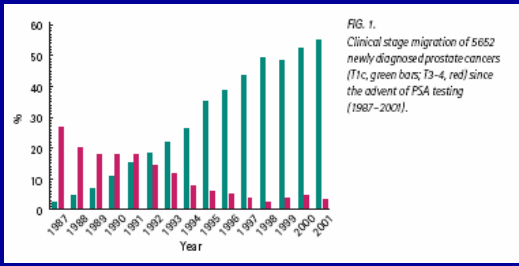
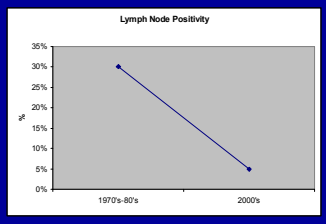
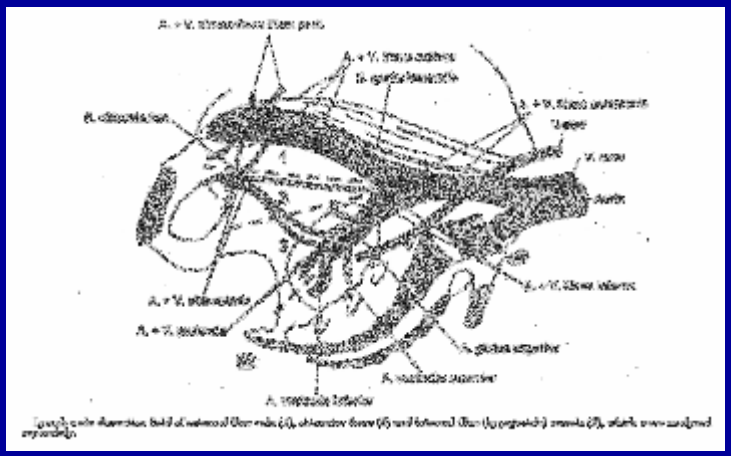


FIG. 1.
Clinical stage migration of 5652 newly diagnosed prostate cancers (T1c, green bars; T3–4, red) since the advent of PSA testing (1987–2001).

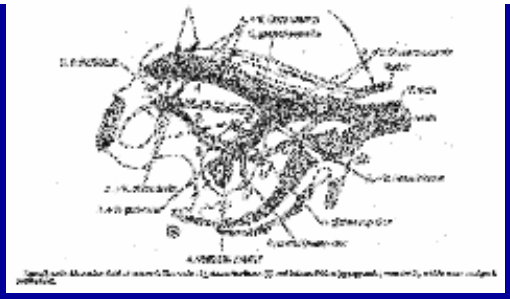


The standard PLND…



Recovers approximately 9 nodes

IS A LIMITED LYMPH NODE DISSECTION AN ADEQUATE STAGING PROCEDURE FOR PROSTATIC CANCER?



365 patients 1989-99

Median PSA 11.9ng/mL (0.4-172)

Number of LN's removed (median) 21 (6-50)

24% (88) positive nodes

Not a typical North American series!

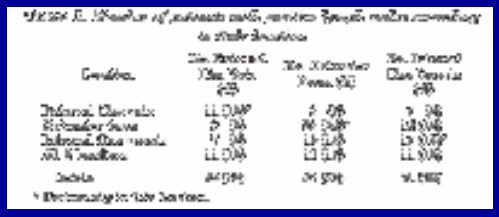
70% ≥pT3

Rate of positive nodes increased with extent of local disease:

TABLE 1. *Pathological tumor stage (TNM 1997)*

Tumor Stage	No. Pts. (%)	No. Pts. With Lymph Node Metastases (%)
pT1	6 (2)	0 (0)
pT2a/2b	204 (56)	26 (13)
pT3a	60 (16)	13 (22)
pT3b	91 (25)	47 (52)
pT4	4 (1)	2 (50)
Totals	365 (100)	88 (24)

Where were the positive nodes?



Internal iliac node positive in 58% of those with positive nodes

Internal iliac nodes alone positive in 19%

2% rate of lymphoceles requiring Rx

Conclusion:

1. The rate of LN involvement is probably under-stated – the harder you look the more you find!

2.Omitting dissection along internal iliac vessels results in under-representative staging

Original Articles

DISEASE PROGRESSION AND SURVIVAL OF PATIENTS WITH POSITIVE LYMPH NODES AFTER RADICAL PROSTATECTOMY. IS THERE A CHANCE OF CURE?

PIA BADER, INGNA G. BURKHARD, REGULA MARKWALDER AND URS E. STUMER

88 patients with positive lymph nodes

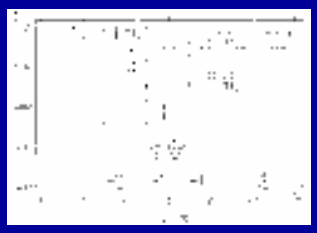
Median FU 45 months

Time to PSA relapse and disease progression related to number of positive nodes

1 positive node(39):	*39%(15) disease free*
2 positive nodes(20):	*10%(2) disease free*
>2 positive nodes(29):	*14%(4) disease free*

Lower PSA relapse rate..

Cancer Specific Survival



Better cancer specific survival..

Summary

The rate of LN positivity is understated

and,

There may be a survival advantage to removal of micrometastatic disease

However,

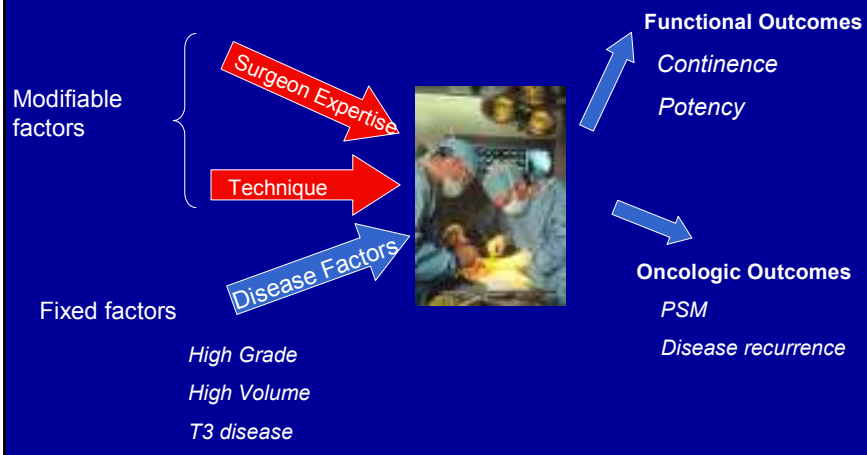
The effect of ***lead time bias*** *cannot be discounted*

Until this is answered,

Does high risk disease deserve an extended dissection?

Modifications to Surgical Technique

Oncologic & Functional Outcomes Directly Related to three variables..

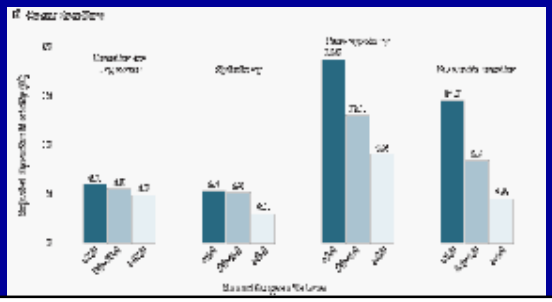


Surgeon Expertise – Volume Matters

>400 000 patients

Medicare claims database

Relationship Between Surgeon Volume & Operative Mortality



Volume and *Function*…

SEER database

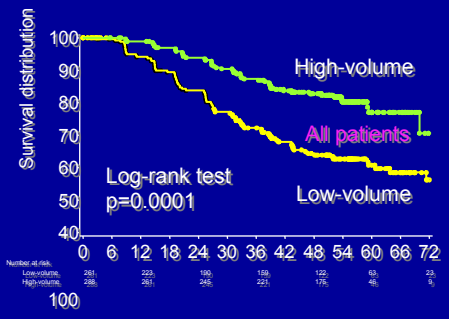
TABLE 4. RELATION BETWEEN SURGEON VOLUME AND OUTCOME AMONG 10,737 MEN WHO UNDERWENT RADICAL PROSTATECTOMY BETWEEN 1992 AND 1996.

OUTCOME	SURGEON VOLUME*				P VALUE	
	LOW (N=642)	MEDIUM (N=198)	HIGH (N=103)	VERY HIGH (N=56)	ADJUSTED FOR CLUSTERING†	ADJUSTED FOR CLUSTERING AND CASE MIX‡
	% of patients					
Surgery-related death						
30 days	0.4	0.5	0.5	0.5	0.71	0.74
60 days	0.5	0.5	0.6	0.6	0.74	0.59
Postoperative complications	32	31	30	26	0.008	<0.001
Late urinary complications						
Symptoms or procedures	28	26	27	20	0.003	0.001
Major events	19	18	17	14	0.01	0.01
Long-term incontinence						
Symptoms or procedures	20	20	19	16	0.08	0.04
Major events	7.3	7.2	6.7	6.6	0.82	0.34

Surgeon & hospital volume independent predictors of functional outcome

Volume and *Oncologic Outcome..*

Canada wide study of 3 vs 8 months of neoadjuvant hormonal ablation prior to RRP



No difference in baseline prognostic factors.

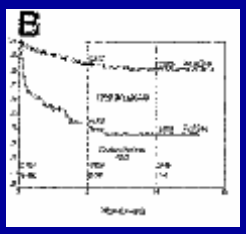
Technique

*Aim to **avoid positive surgical margins** with acceptable functional morbidity*

Because, PSM's matter:

10 year bNED rates:

Negative Surgical Margins	*36%*
Positive Surgical Margins	*81%*



PSM's in association with EC disease are associated with a worse prognosis than those resulting from incision of an organ confined cancer

Technique directed towards excision of *key tumour related anatomic points:*

Several Techniques Recommended to reduce PSM's

- Control of bleeding and maximal exposure to improve visualisation
- Division of 'prostatic pillars' that tether the apex
- Identify the most distal aspect of the prostate – 'beware of the notch'
- Sever recto-urethralis completely to enable entry of correct posterior plane

<u>In high risk disease:</u>

Wide resection of the neurovascular bundle

Complete seminal vesiculectomy beneficial?

Klein et al; 35% bNED @ 13 years for SV+, ECE-ve disease

Avoid a laparoscopic approach?

PSM for pT3 at MSK 17.2% (500cases)

PSM rates for pT3 disease of three large series: 31%

35-60% in smaller series

A low incidence of positive surgical margins in prostate cancer at high risk of extracapsular extension after a modified anterograde radical prostatectomy

Prospective study of 84 intermediate to high risk patients (No cT3's)

56% pT3

13% rate of PSM's

Steps:

1. Endopelvic fscia opened
2. DVC tied but not divided
3. Bladder neck divided
4. Vas deferens divided

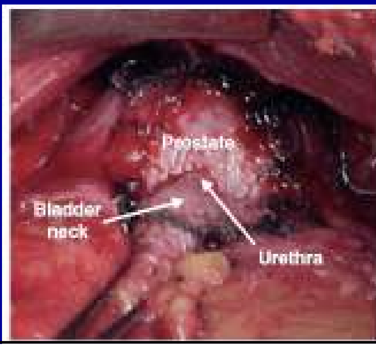
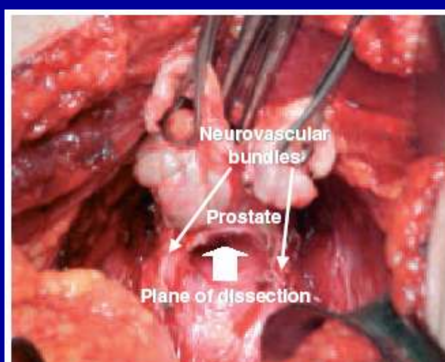


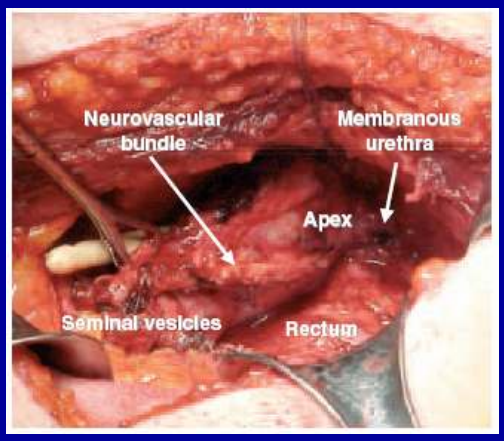
FIG. 1.
Exposure of the base of the prostate with sparing of the circular fibres of the bladder neck.

5. Denonvilliers fascia opened and blunt creation of a plane anterior to the rectum to level of apex

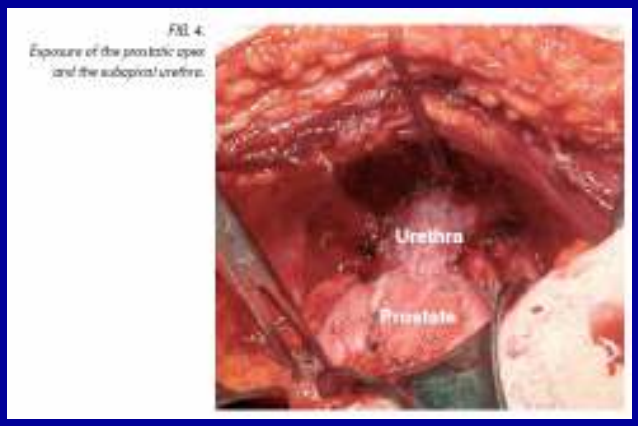


6. Division of neurovascular bundles and pedicles

7. DVC divided



8. Inspection of apex and division of urethra



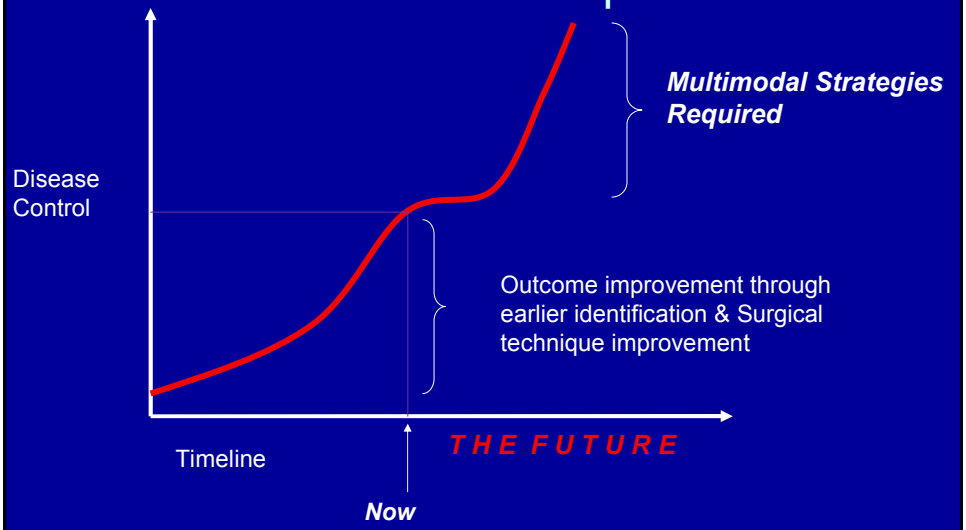
Multimodal Approaches

Neoadjuvant Therapy

Adjuvant Therapy

Timeline

Disease control from incremental Technical advances has plateaued….



Multimodal Approaches

Neoadjuvant Therapy

Timeline

A Role for Neoadjuvant Hormonal Therapy?

Theoretical premise:

→ *'Androgens nourish the prostate'*

Animal studies:

→ *Survival benefit shown*

Clinical observations:

→ *Benefit in metastatic disease*

→ Local tumour response on DRE:

Promising..

But

Does it work?

Studies of NHT

Early non-randomized studies of 3 months of NHT → Beneficial pathologic effects

Phase 3 randomized studies: 3 vs 0 months of NHT → PSM's decreased > 50%

TO determine optimum length of NHT:

Phase 2 trial of 8 months of NHT → Longer therapy associated with lower nadir and lower PSM's

Studies of NHT

Phase 3 Multi-centre study of 3 vs 8 months of NHT → PSM's reduced by 50% in 8 month group

No significant difference in PSA recurrence rates at 5 years

However,

Subgroup analysis:

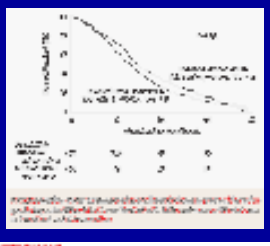
Benefit in PSA recurrence seen in intermediate risk patients operated on at large institutions

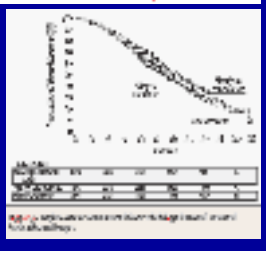
Neoadjuvant Chemotherapy ..?

SWOG 9916

TAX 327

***2 months survival benefit* in metastatic HRPC**





?Benefit in high risk localised disease?

Phase 2 Trials: assess *Safety and Feasibility*

Several Phase 2 trials of neoadjuvant chemo-hormonal therapy prior to RP

Largest trial run out of VGH/BCCA:
- 72 high risk patients, weekly docetaxel plus ADT over 24 weeks

Results Summary:
- **Primary endpoints**
  - Well tolerated
  - Estramustine based regimens increased toxicity

Oncologic Efficacy
- Biochemical Response
  - 24-80% decline in PSA with **chemo alone**
  - Supports anti-tumour activity of chemo without confounding influence of androgen withdrawal
- Pathologic Response
  - Marked tumour regression in some
  - P0 response in few patients

Phase 3 Neoadjuvant Surgical Trial - *Efficacy*

Cancer and Leukaemia Group B (CALGB) Trial 90203

750 men enrolled over 2 years – *still accruing*

High Risk Prostate Cancer

T1-T3a

Nomogram:<=60% probability of BFS at 5 years after surgery

RANDOMIZE

6 Cycles chemotherapy (6 months)

Estramustine days 1-5

Docetaxel every 21 days

Warfarin 2mg daily

Darbopoietin weekly as indicated

\+ Radical Prostatectomy & BPLND

Radical Prostatectomy & BPLND *alone*

Patients observed for 84 months after study closure

Primary Endpoint: 5 year PSA recurrence rates

Multimodal Approaches

Adjuvant Therapy

Timeline

Adjuvant Therapy✓

✓ Confines morbidity of therapy to patients at high risk of relapse based on the most accurate measurement of risk that we have –
pathological assessment of a surgical specimen

✗ Delayed start of systemic therapy if micrometastatic disease present

Radiotherapy

Hormonal Therapy

Chemotherapy

Adjuvant Radiotherapy

3 randomized trials to evaluate this

SWOG Trial

Adjuvant Radiotherapy for pT3 Prostate Cancer

473 patients, Primary endpoint of metastasis free survival

German ARO 96-02 Trial

Adjuvant Radiotherapy for pT3 Prostate Cancer

262 patients, 4 yr FU

Primary endpoint of bNED

EORTC Trial

Adjuvant Radiotherapy for adverse pathological features

1005 patients

Primary endpoint: PSA recurrence

Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911)

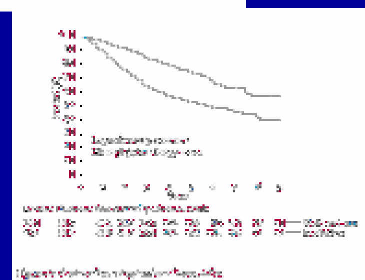
1005 patients

Eligible if 1 or more adverse risk factors:

Capsule perforation

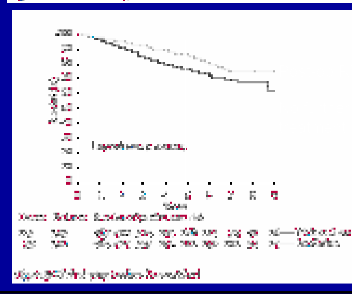
PSM

Seminal vesicle invasion



Randomized → conventional RT (60 Gy over 6 weeks)

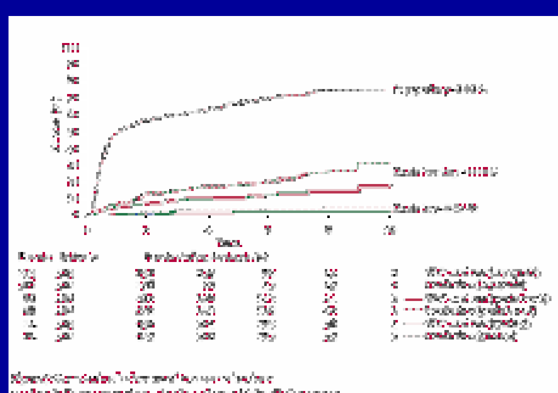
→ wait & see



Primary endpoint: PSA recurrence

Median FU: 5 years

Toxicity of Treatment



Grade 3 or higher toxicity rare; 2.6% in wait & see group

4.2% in adjuvant RT group

SWOG Adjuvant Radiotherapy for pT3 Prostate Cancer. Results of a Randomized, Prospective Clinical Trial

BRFS 60% at 5 years & 49% at 10 years in radiotherapy arm

38% at 5 years & 23% at 10 years in observation arm

HR =.52 (P<0.001)

Survival No difference at 5 years

Trend to better survival in radiotherapy arm at 10 years (74% v. 65%, P=.2)

Time to Hormonal Treatment delayed in radiotherapy arm

Summary Adjuvant EBRT

Risk of PSA recurrence reduced by 21%-26% at 5 & 10 years if poor prognostic factors present

Delays time to hormonal therapy in men who fail adjuvant RT

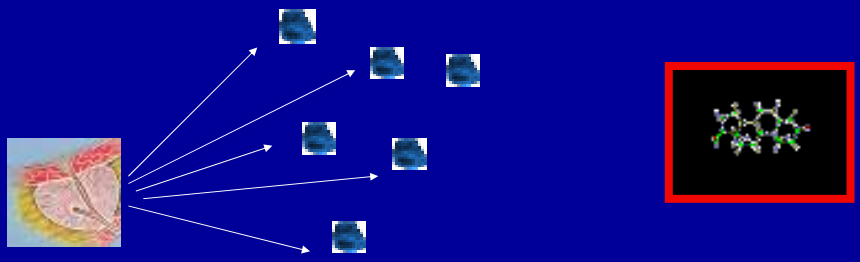
Well tolerated

Consider if adverse pathology with positive margin

But
No survival advantage apparent yet

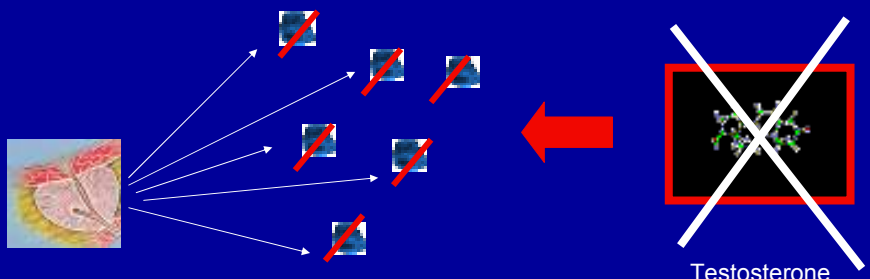
Is it superior to salvage for those who recur?

Adjuvant Hormonal Therapy



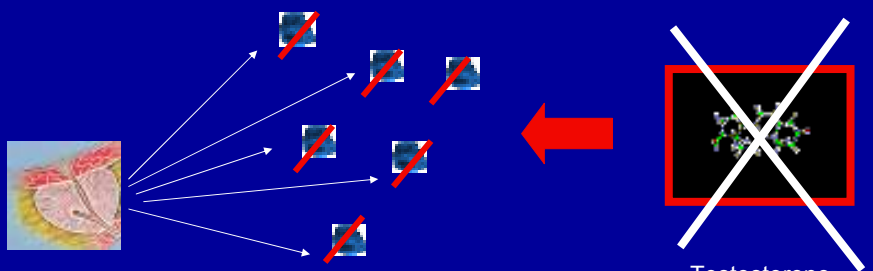
Occult extra-prostatic cancer cells

Adjuvant Hormonal Therapy
The Premise



Occult extra-prostatic cancer cells

Adjuvant Hormonal Therapy
The Premise



Occult extra-prostatic cancer cells

Supported by trials of adjuvant tamoxifen in breast cancer:
reduced recurrence and mortality

And by adjuvant androgen ablation following RT in prostate cancer

Adjuvant Hormonal Therapy
post RP – 4 trials

Adjuvant Goserelin compared to observation

ECOG 7887
98 men
N+ disease post RP
FU 7.1yrs
Messing et al, NEJM 1999

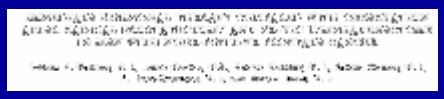
Prayer Galetti et al 2000
T3 disease
FU 5 yrs

Adjuvant Non steroidal Anti-androgens

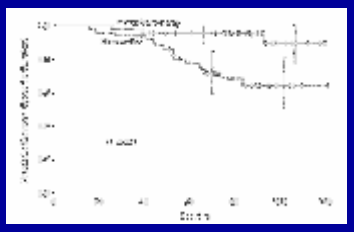
Flutamide vs observation for
pT3 disease
309 men
FU 6.1yrs
Wirth et al Eur Urol 2004

Bicalutamide EPC trial
8113 men

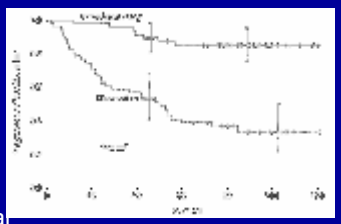
ECOG 7887: *Adjuvant LHRHa Improves Survival*



Prostate Cancer Specific Survival



Progression Free Survival



Overall Survival

Immediate adjuvant hormonal therapy improves survival in node positive disease

EPC- Efficacy of Bicalutamide 150mg for localised or locally advanced CaP. Largest trial of hormonal therapy

North American Trial	Scandinavian Trial	Eur/SA/Aus/Mex
3292	1218	3603

8113 Men

One third T3/4 and one third GG≥7

Randomized, placebo controlled, double blind trial

Bicalutamide 150mg/day or Placebo

plus standard of care (WW, RP, RT)

Primary endpoints: PFS and overall survival

EPC Trial
7.4 year follow-up BJU 2005

In localized disease → ***No Benefit !***

PFS No benefit

Trend towards ***decreased survival in WW group (HR 1.16, P=.07)***

In locally advanced disease

PFS improved for all groups: WW, RT (HR .56) & RP(HR .75)

Overall survival

improved in **RT** group (HR 0.65)

Trend to improved overall survival in **WW** group (HR 0.85)

No survival difference in prostatectomy subgroup

Adjuvant Hormonal Therapy
post RP – 4 trials -? Clinical Utility

Adjuvant Goserelin compared to observation

ECOG 7887

98 men

N+ disease post RP

FU 7.1yrs

Survival benefit shown

(65% vs 85%)

Messing et al, NEJM 1999

Prayer Galetti et al 2000

T3 disease

FU 5 yrs

25.4% improvement in *DFS*

Adjuvant Non steroidal Anti-androgens

Flutamide vs observation for *pT3 disease*

309 men

FU 6.1yrs

No survival benefit

Wirth et al Eur Urol 2004

Bicalutamide EPC trial

8113 men

PFS improved

No survival benefit

Adjuvant Chemotherapy

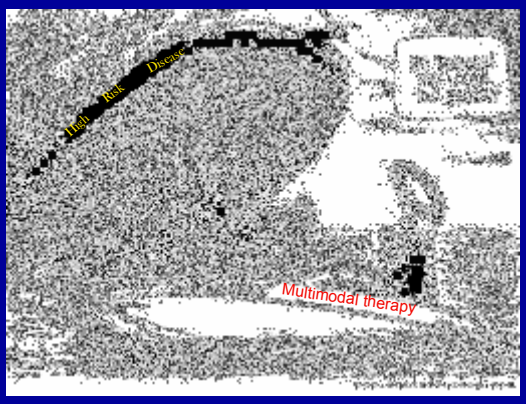
2 small randomized trials of adjuvant Non-docetaxel chemotherapy for high risk disease

National Prostate Cancer Group (Schmidt et al 1993)	Hammersmith Hospital (Wang et al 2000)
184 patients	96 patients, advanced CaP (no mets in 38)
Cyclophosphamide × 2yrs v EMP × 2 yrs v Observation	LHRH + Mitoxantrone vs LHRH alone
Improvement in RFS in EMP group	***Survival advantage shown(80months vs 36 months)***
No Survival difference ?Power	

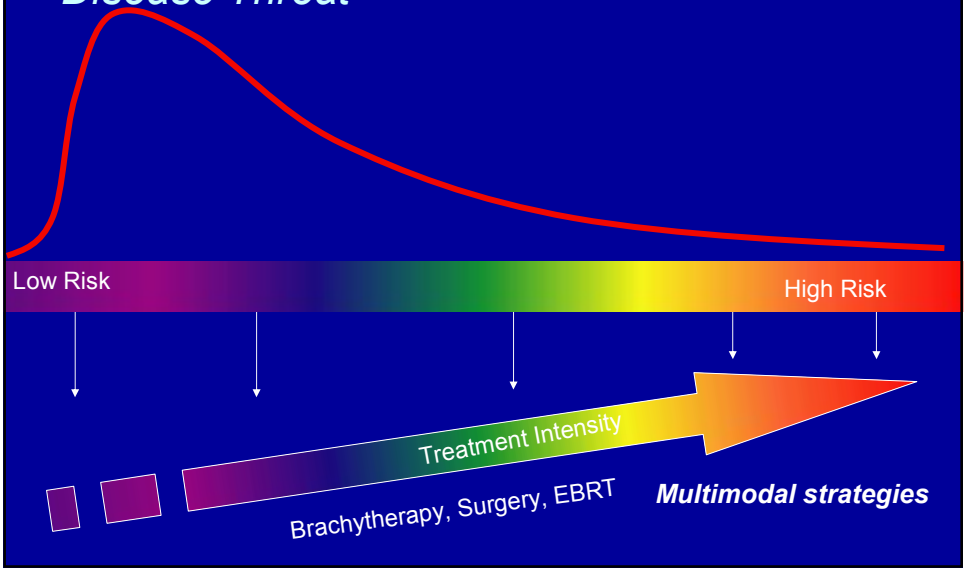
3 Planned/Ongoing Phase 3 Trials of Adjuvant Chemotherapy for High Risk Disease

NCI/SWOG	Sanofi-Aventis	Dept Vet Affairs
CAB × 2yrs v. **Mitoxantrone + Pred + CAB × 2 yrs**	**Observation v.** **LHRH v.** **LHRH + Docetaxel**	**Observation v.** **Docetaxel + Pred**
1360 patients	2171 patients	636 patients
Powered to test for *overall survival*	Endpoint is PFS	Endpoint is PFS @ 5 yrs

The Future – *Matching disease threat to treatment intensity*



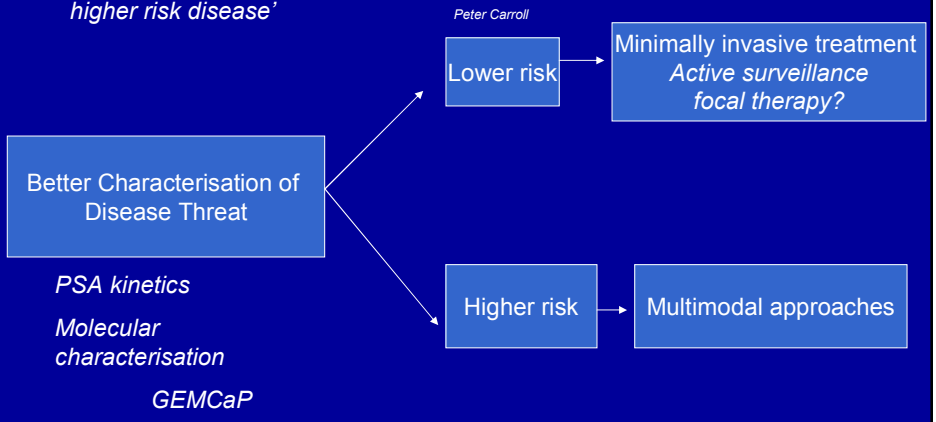
Then we need,
to *better match Treatment Intensity to Disease Threat*



The Future – *Matching disease threat to treatment intensity*

'The battle for prostate cancer will be won & lost in the treatment of higher risk disease'

Peter Carroll



PSA kinetics

Molecular characterisation

GEMCaP

High Risk Disease -The Future

Phase 3 Neoadjuvant Chemo Studies

CALGB 90203

Technical refinements

laparoscopy

3 Phase 3 Adjuvant Chemotherapy trials

Novel therapeutic approaches:

OGX 011

Better Definition of the Efficacy & Role of Multimodal therapies