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PHARMAC Seminars

Prostate Cancer

18 March 2016

Factors influencing management of prostate adenocarcinoma

- History
  - Urological Function
  - Erectile function
  - Bowel Habit
  - Medical co-morbidity
  - Performance status
- Examination
  - PR – prostate mass / Extracapsular spread
    - Not
      - Seminal Vesicle invasion
      - Nodal metastases
  - Distant metastases

- Investigations
  - PSA (normal < 4.0)
  - Doubling time
    - Less 6 months – systemic metastases more likely
  - Biopsy
    - Gleason Score
      - 6, 7, 8-10
    - Percentage involvement
  - Imaging (other than TRUS)
    - Bone Scan / Plain X-ray
    - CT Abdomen/Pelvis
    - MRI
    - NaF PETCT

Prostate cancer staging

- TNM classification
  - T1 a,b,c
  - T2 a,b,c
  - T3 a,b
  - T4
  - N0/1
  - M0/1

- Risk groups
  - Low risk
    - T1-T2a, GS 6, PSA < 10
  - Favourable intermediate
    - T1-T2a, GS 7 (<50% cores), PSA <10 or
    - T1-T2a, GS 6 (<50%), PSA <15
  - Unfavourable intermediate
    - T2b-c, or
    - GS 7, or
    - >50% cores involved
  - High risk
    - T3-4, GS 8 - 10, PSA >20

Role of MRI in staging prostate cancer

- TNM staging
  - T1 a,b,c
  - T2 a,b,c
  - T3 a,b
  - T4
  - N0/1
  - M0/1
- Risk groups
  - Early
  - Favourable intermediate
  - Unfavourable intermediate
  - High risk

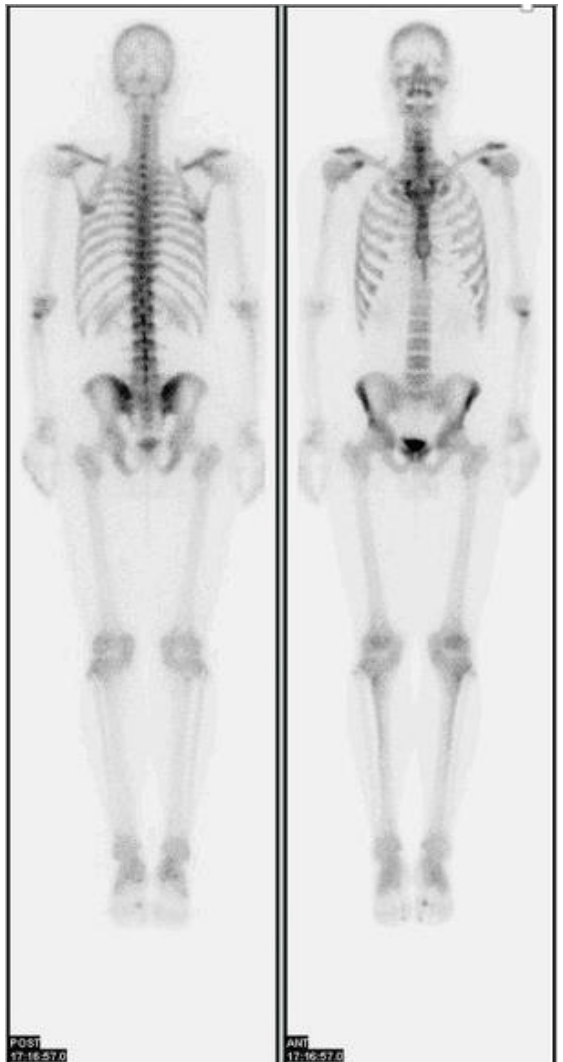
Sensitivity of detecting pelvic lymph node metastases

- Meta-analysis CT vs MRI
- CT
  - Sensitivity 0.42 (0.26–0.56 95% CI)
  - Specificity 0.82 (0.8–0.83 95% CI)
- MRI
  - Sensitivity 0.39 (0.22–0.56 95% CI)
  - Specificity 0.82 (0.79–0.83 95% CI)

➔ The differences in performance of CT and MRI were not statistically significant

Clin Radiology 2008; 63:387–395

Radionuclide scanning in prostate cancer



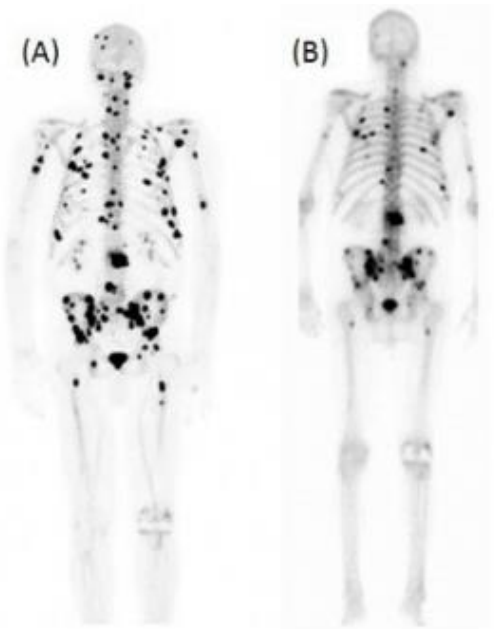
- Often combined with ‘plain imaging’
- Radionuclide ‘Bone scan’
  - ^{99m}Technecium
  - Standard of care
  - Good sensitivity (62 to 82%) for sclerotic bone metastases
  - Note not useful for lytic bone metastases
- SPECT (Single Positron Emission Tomography)
  - Can detect lesions ~ 1cm
  - Sensitivity 92%, Specificity 82%

- Indications
  - Bone pain
  - PSA over 20
  - PSA 10 to 20 and raised ALP
  - High Gleason score (8-10)
  - Locally advanced disease

Positron Emission Tomography (PET) scanning in prostate cancer

- ‘Standard’ FDG (F-18 fluorodeoxyglucose) PET CT
  - Prostate cancer (PCa) not glucose avid
  - Poor sensitivity even in known sclerotic metastases
  - MRI superior
- ^{18}F-Na Sodium Fluoride PET CT scan (Mercy Radiology/CRG)
  - “100%” sensitivity and specificity PETCT (less with PET alone)
  - Nodal metastases – (non) contrast CT scan ~62% sens, 92% spec

- ProstaScint SPECT
  - Murine monoclonal antibody
  - Reacts against prostate-specific membrane antigen (PSMA)



Comparison of (^{11}C) choline-PET/CT, MRI, SPECT, and bone scintigraphy (BS) in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis

- Pooled sensitivities:
  - Choline PET/CT 0.91 [95% confidence interval (CI): 0.83-0.96],
  - MRI 0.97 (95% CI: 0.91-0.99),
  - BS 0.79 (95% CI: 0.73-0.83)
- Pooled specificities for detection of bone metastases
  - Choline PET/CT 0.99 (95% CI: 0.93-1.00),
  - MRI 0.95 (95% CI: 0.90-0.97),
  - BS 0.82 (95% CI: 0.78-0.85)

Skeletal Radiol. 2014 Nov;43(11):1503-13

Early Prostate Cancer

Management options

Non-intervention management prostate cancer

Watchful Waiting

- Regular PSA testing
- No biopsy

➔ Institution of hormone therapy at symptoms or PSA > 10

Indications

- T1c, PSA slowly rising
- Gleason Score (GS) 6
- (‘Elderly man’)significant medical co-morbidity – therefore limited life expectancy
- Patient choice

Active Surveillance

- 3 monthly PSA
- Repeat TRUS biopsy every two years

➔ Will institute curative treatment

Indications

- T1c and
- GS 6 or less and
- PSA less than 10 and
- Patient preference

Low risk prostate cancer treatment options

Surgical

T1 (T2a)

- Radical Prostatectomy

GS 6

- Robotic-assisted Laparoscopic Prostatectomy

PSA <10

Radiation Therapy (RT)

- ^{125}Iodine seed implant
  - Low Dose Rate (LDR) brachytherapy
  - Private only
- Radical Volumetric Modulated Arc Therapy (VMAT)
  - Form of Intensity Modulated Radiation Therapy (IMRT)
  - 74Gy in 37 fractions
- High Dose Rate (HDR) brachytherapy alone
  - Not currently offered in Australasia

Low risk prostate cancer treatment outcomes

Surgery vs RT

T1 (T2a)

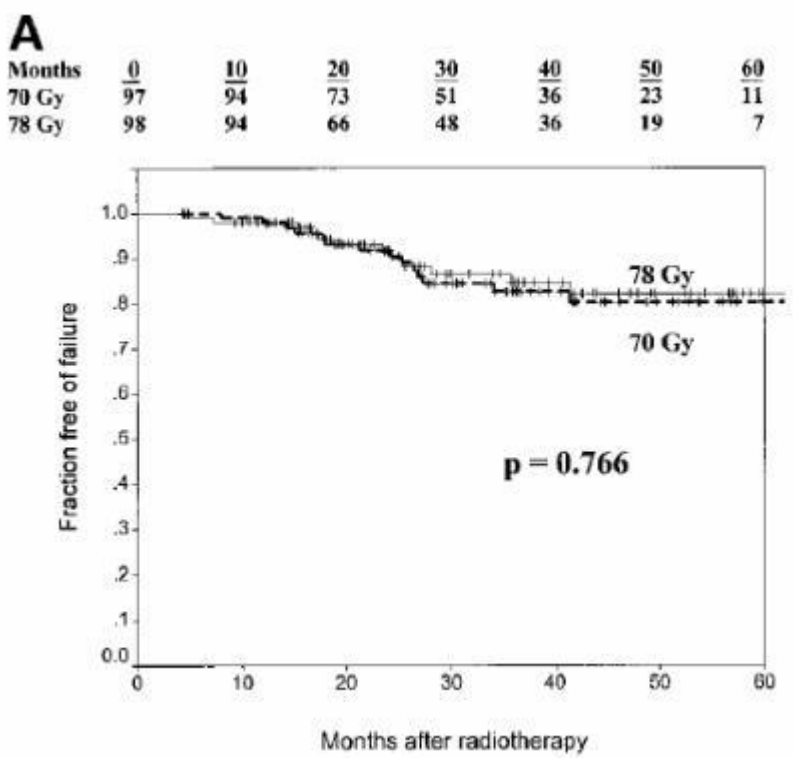
GS 6

PSA <10

- Never been Randomised Controlled Trial (RCT)
- Retrospective review 2991 patients T1-T2a prostate cancer comparing
  - prostatectomy,
  - RT <70Gy, RT >70Gy
  - LDR brachytherapy (+/- XBRT)
  - No difference (except RT <70Gy)

Int J Rad Oncol Biol Phys 2000; 46: 567 - 74

Radiation Therapy (RT)



JAMA 2005; 294: 1233 - 9

Favourable intermediate risk prostate cancer treatment options

Surgery

T2a
GS 7 <50%
PSA <10

- Radical Prostatectomy

or

- Robotic-assisted Laparoscopic Prostatectomy

T2a
GS 6 <50%
PSA < 15

Radiation Therapy

- VMAT IMRT 78Gy
  - Prostate and lower Seminal Vesicles

Unfavourable intermediate risk prostate cancer treatment options

Surgery

T2b-c
or
GS 4+3 = 7
or
Over 50%
cores
involved

- Neoadjuvant Hormone Therapy?
- Radical Prostatectomy
- Robotic-assisted Laparoscopic Prostatectomy

PSA 15 - 20

- Adjuvant or Salvage Radiation Therapy (64Gy)
  - T3, positive margins
  - Rising PSA

Radiation Therapy

- 6 months neoadjuvant hormone deprivation – LHRH agonist

then

- VMAT IMRT 78Gy
  - Prostate and Seminal Vesicles
- External beam and HDR brachytherapy boost

consider

- Adjuvant hormone deprivation

Unfavourable intermediate risk prostate cancer evidence

Surgery

T2b-c
or
GS 4+3 = 7
or
Over 50%
cores
involved

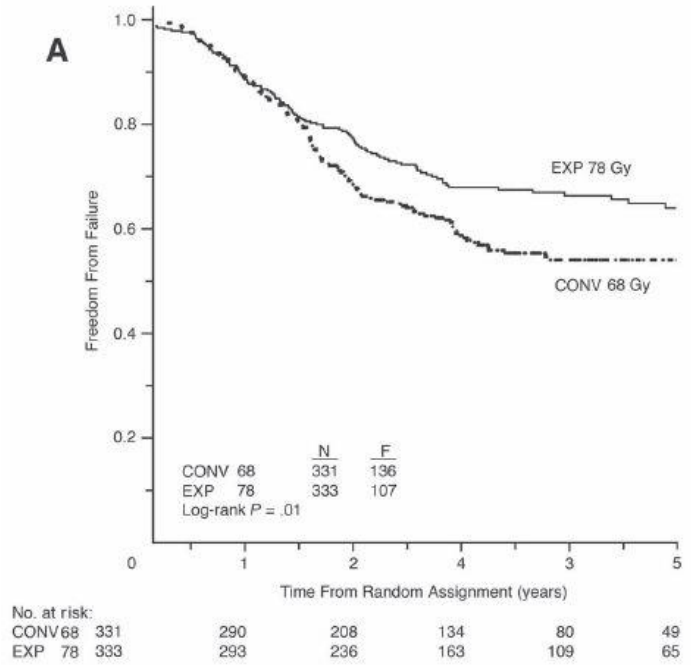
- Neoadjuvant Hormone Therapy?
  - 3 months – less positive surgical margins but no difference in biochemical recurrence at five years
  - J Urol 2002; 167: 112-6
  - Clin Urol 2003; 170: 791-4

PSA 15 - 20

- Adjuvant or Salvage Radiation Therapy (64Gy)
  - RAVES trial – 333 men
    - Closed recruitment 31/12/2015

Radiation Therapy

- 78Gy better than 70Gy – three RCTs



Peeters JCO 2006; 24: 1990-6

External Beam RT and HDR Brachytherapy

- Indications
  - Intermediate or high-risk prostate cancer
    - T2b or greater
    - PSA > 10
    - GS seven or more
    - Good urine function
      - No previous TURP
    - Small prostate volume

- EBRT 45 to 50.4Gy
- HDR brachytherapy
  - 19.5Gy in three fractions
  - 17Gy in two fractions

- Six months neo-adjuvant hormone therapy
- Adjuvant HT for high-risk

Adjuvant Radiation Therapy

- RAVES trial
  - Await results
- Watchful waiting
  - Aim for salvage RT
  - Ideally PSA < 0.3

- Indications
  - Extra-prostatic extension
  - Seminal vesicle invasion
  - Positive resection margins
  - No evidence lymph node involvement
  - Undetectable PSA
  - ECOG 0 – 2
  - Ideally within four months radical prostatectomy

Efficacy of Adjuvant Radiation Therapy

- Three RCTs shown improvement in biochemical progression-free survival, compared to observation
- EORTC 22911 – improved biochemical progression free survival at 5 years, 74% vs 52.6% p<0.0001
- SWOG 8794 – improved biochemical progression free survival at 10 years, 64% vs 34.9%, p<0.001
  - The median biochemical progression free survival was increased from 3.1 years to 10.3 years
  - Non-significant trend to improved metastasis free survival
- EORTC 22911 - beneficial clinical progression-free survival and local failure
- No survival benefit demonstrated yet

- Toxicity
  - EORTC 22911 – see 'fig 5'
    - No difference grade 3 or 4 late toxicity
- Quality of Life
  - SWOG 8794 assessed – final report awaited

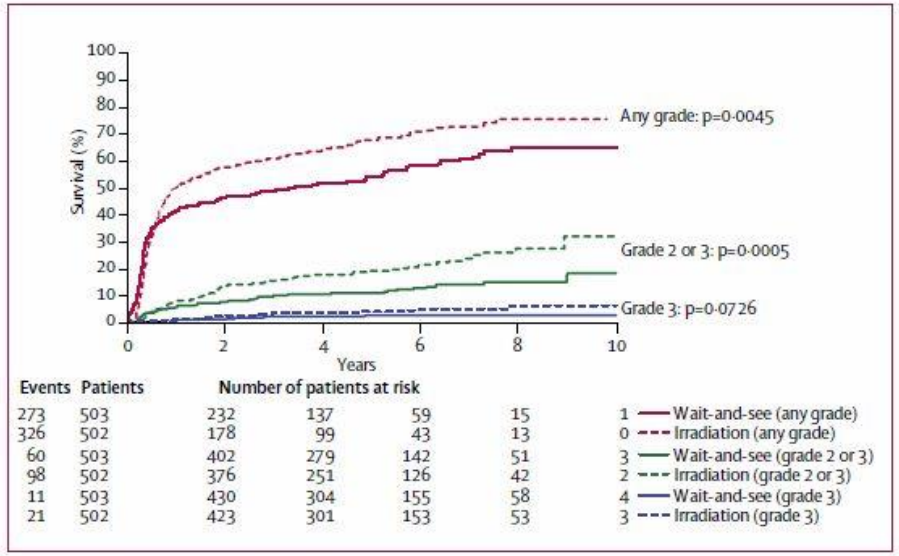


Figure 5: **Cumulative incidence of late complications**
p values indicate comparison of wait-and-see with irradiation groups.

High risk prostate cancer management

Surgery

T3/4
or

- Adjuvant or Salvage Radiation Therapy (64Gy)

GS 8-10
or

PSA > 20

Radiation Therapy

- 6 months neoadjuvant hormone deprivation – LHRH agonist

then

- VMAT IMRT 78Gy
  - Prostate and Seminal Vesicles

then

- 12 to 24 months adjuvant hormone deprivation

Bolla, Lancet 2002; 360: 103-6
Hanks, JCO 2003; 21: 3972-8
Horwitz, JCO 2008; 26: 2497-2504
Pilepich, IJROBP 2005; 61: 1285-90
Pollack, IJROBP 2006; 64: 518-26

Adjuvant hormone therapy improves survival in high risk prostate cancer

- Two RCTs have shown significant survival benefit with long-term androgen deprivation for 2-3 years
  - Side effects
    - Cognitive, fatigue, mood
    - Hot Flushes
    - Hypercholesterolaemia
    - Impotence
    - Osteoporosis
    - Weight gain

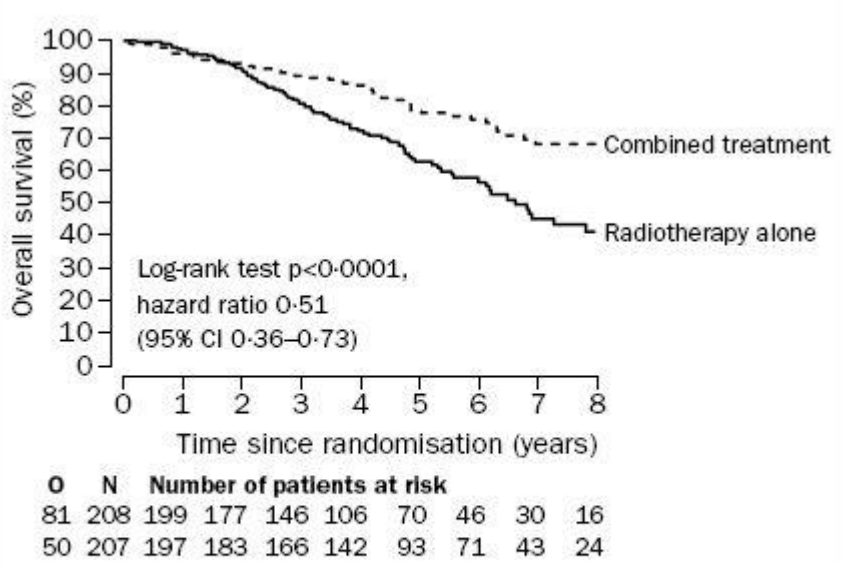
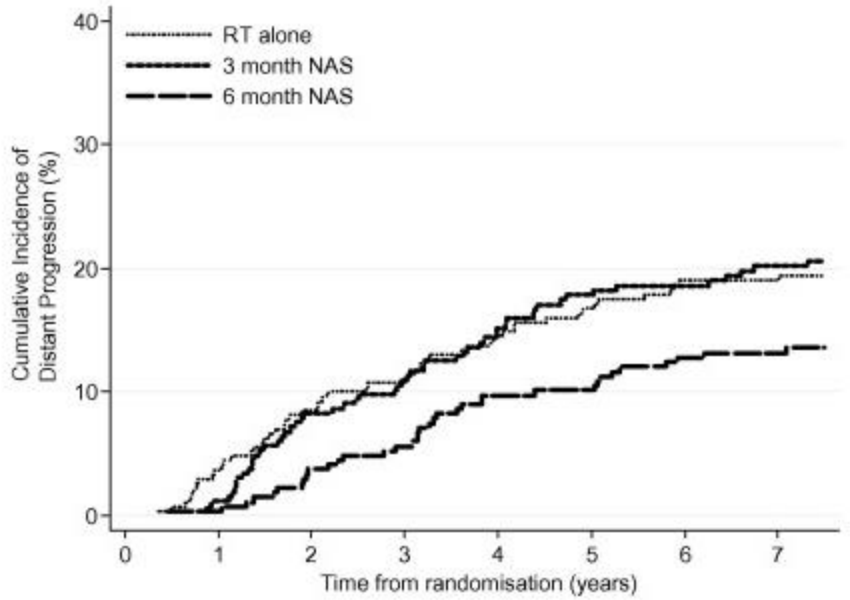


Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**
O=number of deaths; N=number of patients.

Bolla, Lancet 2002; 360: 103-6
Pilepich, IJROBP 2005; 61: 1285-90

Neo-adjuvant hormone therapy (then RT) improves disease control

- TROG 96.01
  - Ph 3 RCT
    - RT alone
    - 3 months NAS then RT
    - 6 months NAS then RT
    - RT dose 66Gy
    - NAS Goserelin, Flutamide
  - 802 men, 7.5 yrs followup



Number of events*

RT alone	10	13	6	10	6	6	0	1
3 month NAS	3	19	7	11	7	2	4	1
6 month NAS	1	9	5	11	1	7	1	1

Fig. 2.
Cumulative incidence of distant progression occurring in the first 7.5 years of follow-up by treatment arm. *Abbreviations:* RT, radiotherapy; NAS, neo-adjuvant androgen suppression therapy. *Number of distant progression diagnosed before secondary therapeutic intervention.

Denham JW Radiotherapy Oncol 2013; 107: 123-8

ENZARAD: Randomised phase 3 trial of Enzalutamide in androgen deprivation therapy with radiation therapy for high-risk, clinically localised prostate cancer

Eligibility

Localised prostate cancer
High risk of recurrence
Suitable for EBRT

Stratification

Gleason score 8-10
T3-4 disease
PSA ≥20 ng/mL
Study Site

R 1:1

Enzalutamide 160mg daily for 24 months
+ LHRHA for 24 months
+ EBRT 78 Gy in 39# starting after 16 weeks

Conventional NSAA for 6 months
+ LHRHA for 24 months
+ EBRT 78 Gy in 39# starting after 16 weeks

Endpoints

Overall survival (primary)
Cause specific survival
PSA progression free survival
Clinical progression free survival
Health related quality of life
Adverse events
Incremental cost-effectiveness

800 participants
2 years accrual + 5.5 years minimum additional follow-up
80% power to detect 33% reduction in the hazard of death from any cause, assuming an OS rate at 5 years of 76% in the control group

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid

Neoadjuvant chemotherapy without androgen deprivation high risk PCa

Neoadjuvant chemotherapy								
Trial	Patients (n)	Regimen	Duration	Outcomes				
				pCR %	PSM %	PFS %	OS	FU (range)
Dreicer et al. (2004) [18]	29	Docetaxel (wkly)	6 Weeks	0	4	71	NR	23 (1.5–36)
Magi-Galluzzi et. al (2007) [19]	43	Docetaxel (wkly)	6 Months			43	NR	49 (23-72)
Febbo et al. (2005) [20]	19	Docetaxel (wkly)	6 Months	0	NR	44	NR	26 (4.5–40)
Friedman et al. (2008) [21]	15	Docetaxel (wkly)	3–6 Months	0	55	38	NR	17 (9–34)
Shepard et al. (2009) [22]	19	Nab-paclitaxel (wkly	2 Months	0	NR	NR	NR	NR
Garzotto et al. (2010) [23]	57	Docetaxel and mitox	4 Months	0	33	50 (5yrs)	NR	63 (7–88)
Layton et al. (2012) [46]	16	Ixabepilone (wkly)	3–4 Months	0	50	NR	NR	NR

Published trials of neoadjuvant targeted agents before radical prostatectomy									
					Outcomes				
Trial	Patients (n)	Regimen	Target	Duration	pCR rate %	PSM %	PFS %	OS %	Followup median (range)
Ross et al. [36]	41	Bevacizumab+docetaxel	VEGF	18 Weeks	0	32	51	NR	NR
Vuky et al. [38]	30	Gefitinib + docetaxel	EGFR	2 Months	0	33	67	NR	28 (10–42)
Febbo et al. [39]	11	Imatinib	PDGFR	6 Weeks	0	NR	NR	NR	NR
Mathew et al. [40]	36	Imatinib + docetaxel + LHRH agonist + AA	PDGFR	18 Weeks	0	18	53	94	39 (NR)
Vuky et al. [48]	6	Docetaxel+GVAX	Immune	3 Months	0	NR	NR	NR	NR

Urol Oncol Seminars and original investigations 2015; 33: 217-225

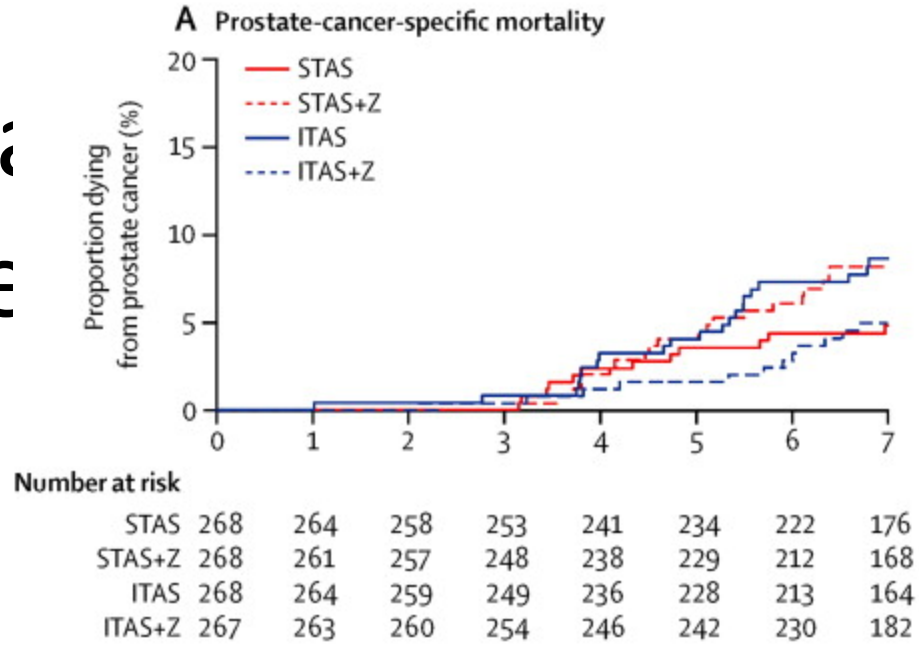
Neoadjuvant chemotherapy with androgen deprivation high risk PCa

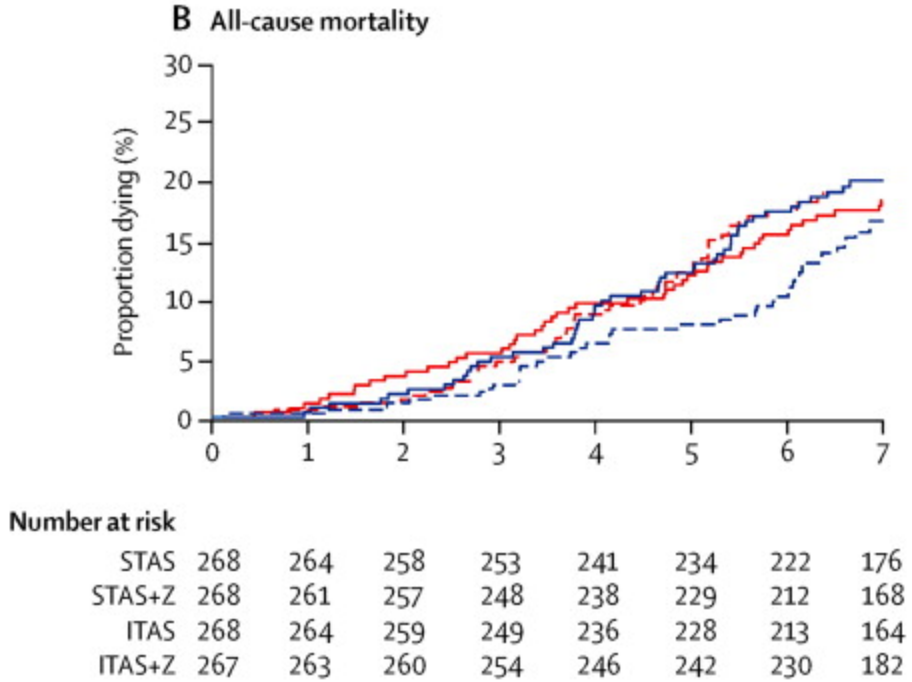
Trials of neoadjuvant chemotherapy with androgen deprivation therapy before radical prostatectomy								
Trial	Patients	Regimen	Duration	Outcomes				
				pCR %	PSM %	PFS %	OS %	Follow-up median (range)
Pettaway et al. (2000) [24]	33	KAVE+LHRH agonist+AA×3 months	3 Months	0	17	69	NR	13 (9–18)
Clark et al. (2001) [25]	18	Etoposide+estramustine	3 Months	0	13	88	NR	14 (5–20)
Hussain et al. (2003) [47]	21	Docetaxel+estramustine	9–18 Weeks	0	30	71	NR	13 (NR)
Konety et al. (2004) [26]	36	LHRH agonist + estramustine + paclitaxel + carboplatin	4–6 Months	0	22	45	NR	29 (5–51)
Silberstein et al. (2014) [27]	34	LHRH agonist + estramustine + paclitaxel + carboplatin	4-6 months	0	24	27	NR	
Prayer-Galetti et al. (2007) [28]	22	LHRH agonist + docetaxel + estramustine	3 Months	5	26	42	NR	53 (30–64)
Chi et al. (2008) [29]	72	LHRH agonist+AA+docetaxel	6 Months	3	27	70	NR	42 (25–66)
Sella et al. (2008) [30]	22	LHRH agonist + AA + docetaxel + estramustine	3 Months	0	27	54	100	23 (12.1–54.7)
Mellado et al. (2009) [31]	57	LHRH agonist+AA+docetaxel	3 Months	6	35	65	NR	35 (23–47)
Womble et al. (2011) [32]	22	Ketoconazole+docetaxel	3 Months	0	42	36.4	NR	18 (3–40)
Narita et al. (2012) [33]	18	LHRH agonist + AA + docetaxel + estramustine	6 Weeks	11	0	77	NR	18 (1–49)

Urol Oncol Seminars and original investigations 2015; 33: 217-225

High risk prostate ca bisphosphonate

- **Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial**
- 2x2 randomisation
- Zoledronic Acid 4mg three monthly – six doses





Denham JW, Lancet Oncol 2014; 15: 1076-1089

Localised prostate cancer treatment – future expenditure

- Imaging
  - MRI resource (DHB)
  - NaF scan?
- Radiation therapy
  - ^{131}Iodine seed implant
  - Stereotactic RT
  - HDR brachytherapy
- Surgery
  - RALRP?
- Systemic
  - Enzalutamide

Other

- Osteoporosis
  - Bone Density Scanning
  - Cholecalciferol
  - Bisphosphonates
- Cholesterol
- Hot Flushes

Recurrent / Advanced Prostate Cancer

Recurrent / Advanced Prostate Cancer

Recurrent post definitive therapy

- PSA rise / failure
- Local recurrence
- Early versus later hormone therapy

Advanced / Metastatic

- Hormone therapy
  - 1st line
  - 2nd line
  - 3rd line – Anne will cover
- Radiation therapy
  - Local
  - Metastatic
- Chemotherapy
- Bisphosphonates

Locally recurrent prostate cancer – following Radiation Therapy

- Salvage prostatectomy
  - Cancer specific survival 83%
  - Very morbid
    - 61% incontinent (Stephenson 2004)
  - European Association of Urology criteria
    - Organ confined <T2b
    - Gleason Score 7 or less
    - PSA 10 or less
- HIFU – High Intensity Focused Ultrasound
  - Promising
  - Needs RCT
- Cryotherapy
  - Potentially curative (Spiess 2013)
    - Biochem DFS 89% @1yr, 66% @3rs
  - Possible side effects
    - 3 to 8.5% urinary retention
    - 4.4-13% incontinence
    - 0-3.3% rectourethra fistula
    - Erectile dysfunction
  - Salvage unifocal cryoablation
- Brachytherapy
  - See over

Feasibility study of a randomised controlled trial to compare (deferred) androgen deprivation therapy and cryotherapy in men with localised radiation-recurrent prostate cancer

- Entry criteria
  - Histologically confirmed prostate cancer post RT/BT
  - Organ confined disease
    - Clinical T1 – T3
    - Radiological confirmation
  - PSA < 20
  - Life expectancy > 5 years

Br J Cancer 2014; 111: 424-9

- 39 patients screened over 18 months
- 28 patients offered randomisation
- 7 agreed to randomisation

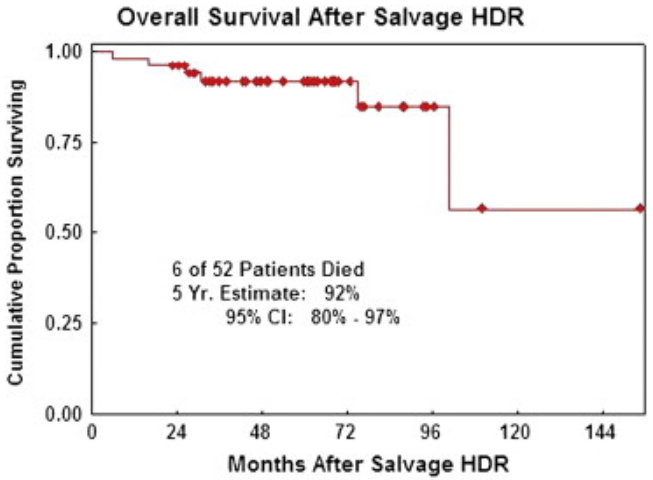
- Cryotherapist Qualification Process difficult

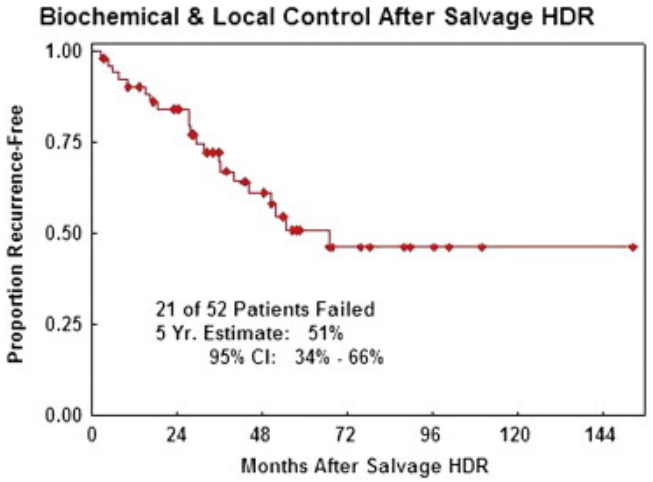
➔ Is a RCT possible?

Brachytherapy for locally recurrent prostate cancer post external beam RT

- Chen et al (incl Mack Roach) IJROBP 2013
  - Retrospective review
  - 52 patients
  - 36Gy in six fractions
  - 24 patients neoadj HT

- 2% late grade 3 GU toxicity
  - No gastrointestinal

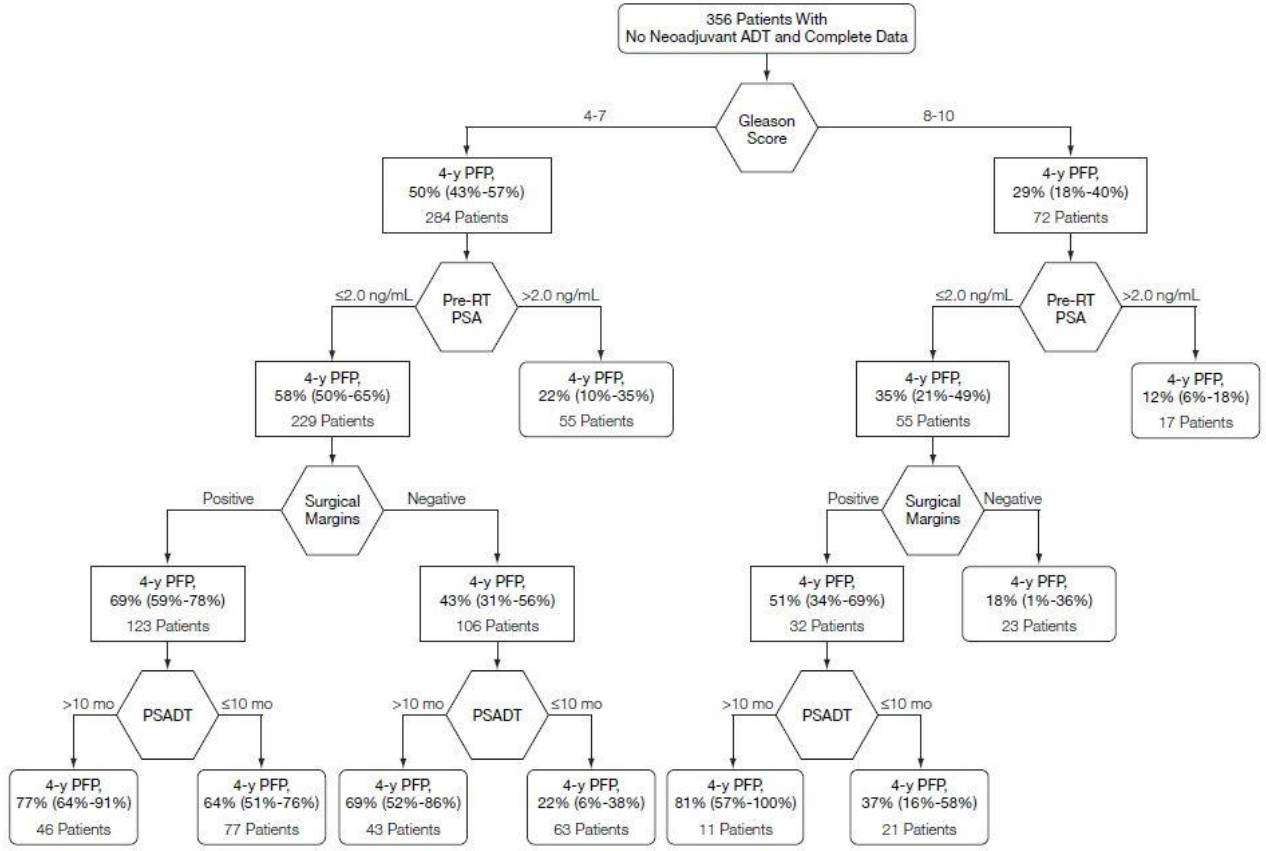




Locally recurrent prostate cancer – following Radical Prostatectomy

- Salvage Radiation Therapy (64Gy)
  - Indications
    - Persistent PSA > 6 weeks post Prostatectomy
    - Rising PSA from undetectable level
    - (PSA doubling > 6 months)
    - No metastases
    - ECOG 0 – 2

Figure 2. Four-Year Actuarial Progression-Free Probability (PFP) After Salvage Radiotherapy



Progression-free probability (PFP) stratified by Gleason score, preradiotherapy prostate-specific antigen (PSA) level, surgical margins, and PSA doubling time (PSADT). Patients receiving neoadjuvant androgen deprivation therapy (ADT) were excluded from this analysis. All values in parentheses are 95% confidence intervals. RT indicates radiotherapy.

Stevenson JAMA 2004; 291: 1325-32

Watchful waiting at PSA recurrence

- Salvage therapy not possible / declined
  - Watchful waiting standard of care
- Early versus delayed hormone therapy
  - TOAD trial
- When to start hormone deprivation?
  - Factors
    - PSA level – 10 to 20
    - PSA kinetics (doubling time)
    - Tumour parameters
    - Patient preference
    - Physician bias

Castration-naïve progressive prostate cancer systemic options

- Bilateral Orchiectomy
  - Gold standard
  - Day case procedure
- LHRH agonist or antagonist
  - Equally effective
  - Six monthly Eligard 45mg
  - Side effects
- Anti-Androgens
  - Combined androgen blockade
    - Symptomatic disease – start before LHRH agonist
    - Continue 7 days post injection
  - Monotherapy less effective than castration

Timing of androgen deprivation therapy in prostate cancer patients with a rising PSA (TOAD)

- PSA relapse after definitive therapy
  - (Asymptomatic men not for curative treatment)
- Randomised
  - Delayed ADT (arm A)
  - Immediate ADT (arm B)
- 293 patients
  - Median follow up 5.0 years

- Overall survival
  - Arm A 30 deaths, 6yr OS 79%
  - Arm B 16 deaths, 6yr OS 86%
  - HR 0.54 (0.27 – 1.06) p = 0.07
- Local progression
  - HR 0.51 (0.34 – 0.76) p = 0.001
- Distant metastases
  - HR 0.54 (0.32 – 0.90) p = 0.018
- Arm A 34% started ADT < 2 years, 49% started > 4 years

Duchesne GM, JCO 2015; 33, 15_suppl: 5007

Effectiveness of medical or surgical castration

- Profound immediate fall in PSA
  - Often to undetectable levels
- Median failure-free survival ~ one year
  - 11.2 months (5.1 to 28.8)
  - Eur Urol 2015; 67: 1028-38

- Side effects
  - Hot flushes
  - Cognitive, loss drive
  - Mood
  - Impotent
  - Osteoporosis
  - Cholesterol
  - Weight gain

Intermittent versus continuous ADT

- Systematic review of randomised controlled trials
  - 9 trials, 5508 pateints
  - Overall survival
    - HR 1.0 (0.94 – 1.11) for IAD
  - Progression free survival
    - HR 0.96 (0.76 – 1.20) for IAD

JCO 2013; 31: 2029-36

- IAD superior
  - Sexual function
  - Physical activity
  - General well-being
  - 48% cheaper
- But…
  - Maha Hussain (JCO 2015; 34: 280-5) reviewed five trials and found IAD not superior to CAD…

Intermittent versus continuous ADT SWOG 9346 trial

- Metastatic patients
  - End point overall survival
  - 3040 men newly diagnosed metastatic disease and PSA 5 or more
  - If PSA declined to <4 randomised to iADT (770 men) or cADT (765)
  - iADT – stopped at that point ? when < 4
  - ADT restarted when PSA increased to 20, or previous baseline PSA, or symptoms

- ADT
  - Goserelin 10.8mg 3 monthly
  - Bicalutamide 50mg od
- Not finally published
  - Presented at ASCO
  - Median follow-up 9.2 years
  - iADT median OS 5.1 years
  - cADT 5.8 years
  - HR 1.1 (0.99 – 1.23)
  - All subgroups cADT slightly better

ASCO 2012

Docetaxel in castration-naïve metastatic prostate cancer

- French GETUG-15
  - No OS benefit
  - Lower metastatic burden
- CHAARTED
  - Improved OS
- STEMPEDE

➔ Anne will discuss

- High-volume definition as per CHAARTED
  - Visceral (lung/liver) and/or
  - Four or bone metastases, at least one beyond pelvis and vertebral column

- Note: different definitions of high-volume disease

Prostate radiation therapy in advanced disease

- Local RT useful in controlling local symptoms when castrate resistance occurs
- Indications
  - Low metastatic burden (oligo-metastastic)
  - Good life expectancy / performance status
  - Good response to ADT
  - ? Timing – usually symptomatic at PSA

- RT for oligo-metastatic disease
  - 3 metastases or less
  - No RCT data
  - Might offer improved DFS / OS in addition to ADT
  - Stereotactic Body RT (SBRT)

PSA or symptomatic progression on continuous ADT

- Residual androgen production by adrenals may stimulate PCa when on LHRH agonist
  - Test testosterone?
- Combined/Maximal androgen blockade
  - Add Bicalutamide 50mg
  - Short PSA response – months usually

➔Then Abiraterone when symptomatic

Post-Chemotherapy
- ECOG 0-2

No chemotherapy
- ECOG 0-1

Management non-metastatic castrate-resistant prostate cancer

- Micro-metastases missed on current imaging modalities
  - NaF PET/CT?
  - What to do with result
- Time to first bone metastasis 40.8 months
  - 26 months PSADT <10mths
  - 18.5 months PSADT <4 mths

- No RCT data on Abiraterone or Enzalutamide currently

- Three large RCTs assessing M0 CRPC

Palliative Radiation Therapy

- Common intervention
- PCa metastases mostly to bones
- Fractionation schedules
  - 20Gy in five fractions
    - Longer time till retreatment
  - 8Gy single fraction
    - Slightly quicker onset pain relief
  - (30Gy in ten fractions)

- Retreat
  - Same site can be retreated once
  - SC-20 trial – no difference retreat fractionation schedule
    - Lancet Oncol 2014; 15:164-71

- Hemi-body RT
  - 6Gy upper hemibody
  - 8Gy lower hemibody
  - Sequential – six weeks between

Radionuclide treatment

- Strontium-89
  - Useful for widespread bone metastases – not super-scan
  - No survival advantage – pain relief and increased time to next SRE
  - Good renal function
  - Risk pancytopenia
  - Flare in pain
- Radium-223
  - Extend life in CRPC with symptomatic bone (no visceral/ bulky nodal) metastases
  - Can repeat
  - Investigated with denosumab and Zoledronic acid – increased OS benefit remains
  - Trials on-going in combination with other agents

Bisphosphonates

- CALGB 90 202 trial
  - Zoledronic acid in castration naïve bone mets
  - No difference in time to first Skeletal related event (SRE)
- Note Denosumab not tested for reducing SREs in castration-naïve
- Zoledronic acid for painful bone metastases
  - JNCI 2002; 108:1458-68
    - Significant delay in time to next SRE
- Denosumab versus Zoledronic acid CRPC
  - Lancet 2011; 377: 813-22
  - Median time to SRE
    - Denosumab 20.7 months
    - Zoledronic acid 17.1 months
    - HR 0.82 (0.71-0.95) p = 0.0002

Other interventions

- Exercise
  - Resistance exercise and moderate to strenous physical activity
  - improves fitness and
  - reduces fatigue and impact on daily living
    - Psycho-Oncology 2006; 15(10):847-862
    - JCO 2003; 21(9): 1653-1659
    - Cancer 2004;101(3):550-557
- Depression and anxiety
  - Psychosocial support
- Osteoporosis
  - Consider length ADT
  - Bone Density Scan
  - Bisphosphonates
- Dexamethasone
  - Indications
    - Flare RT
    - PSA progression
    - End of life