

FINGERTIP UROLOGY – PERTINENT POINTS

PROSTATE CANCER

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1. Background statistics

- 1 in 7 American men will be diagnosed in their lifetime ¹
 - men with an affected father or brother are twice as likely to develop prostate cancer as men with no affected relatives ².
 - Significant reductions in prostate cancer mortality over the past decade or so in UK, USA, Austria, Italy, France, Canada, Spain, Germany & Australia with downward trends in Netherlands, Ireland & Sweden ³
 - 80% diagnosed now in most western countries have clinically localised disease ⁴⁻⁶ but ~25% of patients with clinically localised tumours have occult metastases which declare themselves subsequently ⁷
 - Premature death from prostate cancer is much higher for men diagnosed in their 50s compared with those diagnosed in their 70s
 - 60% for men diagnosed in their 50s
 - 50% for men diagnosed in their 60s
 - 38% for men diagnosed in their 70s ⁸
 - Age is not a significant prognostic factor in terms of aggressiveness of tumours ⁹
 - “Appropriate treatment implies that therapy be applied neither to those patients for whom it is unnecessary nor to those for whom it will prove ineffective” (Whitmore 1973) ¹⁰
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2. Whether or not to diagnose prostate cancer using serum PSA

- Screening recommendations vary from country to country but overall do not support population screening ¹¹
- Benefits of screening in improving survival are yet to be proven ¹²
- Therefore, it is advised that men be informed of management options with the benefits and risks of detection so each can make a reasoned choice consistent with his own personal preferences and values
- Clinical ideal of shared decision making but 8-58% of men prefer a passive decision-making role ¹³⁻¹⁶

Appendix 1: check lists

3. Methods leading to biopsy diagnosis

(a) PSA

- Age-based PSA references - see Appendix 2

NON-PROSTATE CANCER CONTRIBUTORS TO INCREASES IN PSA

- Benign prostatic hyperplasia (BPH)
- Ejaculation (both free & total) up to 48 hours
- Bacterial infection of prostate
- Prostatic massage
- Instrumentation (including catheterisation) of prostatic urethra
- Prostatic biopsy

http://ncci.org.au/services/prostate_GPresources.htm

Only about 1 in 3 men with a PSA between 4 & 10 ng/ml have cancer diagnosed – but the proportion depends on population tested and the level of PSA, with an increased likelihood of prostate cancer the higher the PSA

Finasteride reduces serum PSA levels by ~50%

- An elevated PSA can precede

Presence of a palpable nodule or mass by up to 10 years ^{23, 37, 38}

Tumour-induced symptoms by 5-10 years

Death by prostate cancer by 17 years (on average) ³⁹

AUA guidelines recommend biopsies for PSA >4 ng/ml ²⁰

- PSA levels <4 ng/ml

15% of prostate cancers detected between 3 & 4 ng/ml had extraprostatic growth ⁴⁰

In Tyrol project >¹/₃ of prostate cancers detected with PSA 2-3.9 ng/ml and, of these, 24% had a Gleason score ≥7 ⁴¹

Hessels et al (2004) reported that the negative biopsy rate was ~70-80% for a lowered PSA threshold of 3 ng/ml for biopsies ⁴²

No cut-point for PSA with a high sensitivity and specificity in diagnosis of prostate cancer but rather a continuum of prostate cancer risk at all values (Prostate Cancer Prevention Trial) ⁴³

- **A PSA <1 ng/ml in an untreated man**

Indicates a very low risk of cancer so he could be scheduled safely for 3 yearly ⁴⁴ or 8 yearly ⁴⁵ intervals for review

- **Free:total PSA levels in serum** ^{39, 46}

Most useful for serum PSA values between 4 & 10 ng/ml

The higher the free component, the lesser the likelihood of cancer

- **PSA velocity**

A PSA increase >0.75 ng/ml in year = an increased risk of cancer ⁴⁷

PSA increases at ~3.3% pa – if rate of increase is greater, the risk of cancer is greater ²¹⁻²⁴

A PSA increase >2 ng/ml in the year before diagnosis of cancer is associated with a particularly high risk of death from prostate cancer despite radical prostatectomy ⁴⁸

- **PSA density (PSA divided by prostate volume determined by TRUS)**

The larger the transition zone (the site of BPH & the origin of ~25% of cancers), the lower the likelihood of prostate cancer

>0.15 ng/ml per gram is considered worrisome for prostate cancer

(b) DRE

30-50% solitary nodules reported historically to have cancer ⁴⁹

25% of cancers detected in men with normal PSA levels see Appendix 2a ⁵⁰

(c) Prostatic fluid (not routine)

Assay for PCA3/DD3 RNA in urine immediately after DRE is available www.bostwicklaboratories.com but is not yet routine ⁵¹⁻⁵³

Overall sensitivity & specificity were 66% & 89% respectively

- For PSA levels <4 ng/ml, sensitivity & specificity were 74% & 91% and
- For PSA levels 4-10 ng/ml, sensitivity & specificity were 58% & 91%, respectively ^{20, 53}

(d) Prostate biopsies

- **Numbers of biopsy cores**

Sextant biopsies – chance of missing cancer ~25% ⁵⁴

8 & preferably 10 or more recommended & directed laterally with inclusion of antero-lateral horns of peripheral zone ⁵⁵⁻⁶¹

- **Repeat biopsies for suspected cancer**

diminishing returns especially after 3 biopsy sessions: Djavan et al (2001) reported cancer detection rates of 22%, 10%, 5% & 4% with 1-4 biopsy sessions with 58%, 60.9%, 86.3% & 100%, respectively, having organ-confined disease ⁵⁷

Yanke et al (2005) have proposed a nomogram (as an extension of Kattan nomogram) to predict the likelihood of a positive finding following subsequent biopsies ⁶²

- **Prophylaxis**

Peri-operative antibacterial prophylaxis & a pre-procedural enema are routine +/- local or general anaesthesia/sedation

- **Morbidity**

Minor morbidity is common: >50% experience haematuria, haemospermia or blood PR with some men having difficulty voiding following TRUS biopsies. Life-threatening sepsis is <1%

4. Gleason Grading System – see Appendix 3 for criteria

(a) Gleason scoring

- The sum of the Gleason numbers accorded to the dominant & subdominant grades constitute the Gleason score (below). A Gleason number of 4 (as part of the sum) indicates a poorer prognosis ^{61, 62}

(b) PIN

- Prostate intra-epithelial neoplasia (PIN) is believed to be a precursor of cancer in a proportion of patients: 80% of prostates with cancer also contain high grade PIN ^{20, 63}. A finding of PIN usually = a need for further biopsies

(c) Atypical small acinar proliferation

- The reporting of atypical small acinar proliferation indicates a need for further biopsies as 34-60% have cancers in repeat biopsies ⁶³⁻⁶⁶

(d) Grade & prognosis

- without treatment with curative intent, the risk of dying from prostate cancer following diagnosis for
 - Gleason 2-4 tumours is minimal at 20 years
 - Gleason 5-6 tumours is intermediate
 - Gleason 8-10 tumours is high within 10 years ⁶⁷
 - Disease-specific 5 year survival for poorly differentiated cancer was 63-69% using SEER database ⁶⁸
-

5. Prostate cancer staging classification

UICC TNM staging classification	
Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable not visible by imaging
T1a	Incidental tumour in < 5% of TUR tissue
T1b	Incidental tumour in > 5% of TUR tissue
T1c	Needle biopsy prompted by elevated PSA
T2	Organ confined
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends beyond the prostatic capsule
T3a	Extracapsular, unilateral and bilateral
T3b	Tumour invades seminal vesicles (s)
T4	Tumour invades bladder neck, sphincter, rectum, pelvic side wall
Lymph Nodes	
Nx	Regional nodes were not assessed
N0	No regional nodes
N1	Regional node metastases
Distant Metastases	
Mx	Regional nodes not assessed
M0	No Metastases
M1	No distant
M1a	Non-regional lymph nodes
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

6. Clinical assessment following biopsy-confirmation of cancer

(a) DRE by itself is a poor indicator of stage

- Only 52% of 565 men with cT2 on DRE had organ-confined tumour at radical prostatectomy ⁶⁹
- Only 19% of 36 men with cT3 on DRE had organ confined tumour at radical prostatectomy ⁶⁹
- Palpable disease at apex is often indicative of extra-prostatic extension foreshadowing a positive surgical margin or a poorer result following radiotherapy ⁷⁰⁻⁷²

(b) PSA & disease status

- <10 ng/ml - 70-80% will have organ-confined disease
>10 ng/ml - ~50% will have organ-confined disease
>50 ng/ml - ~25% will have organ-confined disease ⁷³
- 10-15ng/ml – 37.5% had evidence of extra-capsular disease
15 ng/ml – all had evidence of extra-capsular disease ⁷³
- <10 ng/ml – 7 year disease-free survival 76-93% ⁷⁴
>10 ng/ml - 7 year disease-free survival 51% ⁷⁴

(c) TRUS biopsy understates Gleason score, stage & prognosis

- Up to 50% with clinically organ-confined lesions are discovered to be understaged following radical prostatectomy ^{7, 75-79}
- Approximately 25% with clinically localized disease experience an early relapse despite successful treatment of the primary lesion ⁷
- Using Epstein et al's 1994 criteria to identify clinically insignificant tumour (viz. PSA density <0.15, Gleason score ≤ 6 with fewer than 3/6 biopsy cores positive & with <50% of the cores involved) Bastian et al reported that 9.7% had Gleason 7 or 8 tumours & 8.4% had non-organ confined disease in 237 patients who underwent radical prostatectomy ⁸⁰
- Gleason 6 tumours: 24% risk of capsular penetration & 29% probability of positive surgical margins ⁸¹

Gleason 7 tumours: 62% risk of capsular penetration & 48% probability of positive surgical margins ⁸¹

Gleason 8-10 tumours: 85% risk of capsular penetration & 59% probability of positive surgical margins ⁸¹

- Gleason 8-10 tumours: 92% had extraprostatic disease ⁶⁹

(d) Partin tables for predicting pathological stage – see Appendix 4

Validated in multicentre studies ⁸² but may not be as useful for tumours arising in the transition zone ⁸³

7. Treatment options for clinically localized disease

(a) Does treatment make a difference?

Bill-Axelsson et al (2005) randomized 695 men to radical prostatectomy or watchful waiting between October 1989 & February 1999. The radical prostatectomy group had a reduced disease-specific and overall mortality & risk of metastases and local progression although

- Only 11.6% (81/695) had cancer diagnosed as a result of a raised PSA
- 48% (334/695) had a serum PSA ≥ 10.1 ng/ml at baseline
- 27.9% (194/695) had Gleason scores ≥ 7 ng/ml
- 11.36% (79/695) diagnosed by cytology or biopsy specimen could not be retrieved ^{84, 85}

(b) Initial treatment options: choice is a 'trade-off' of side-effect risks with one form of therapy compared with those with other therapies

- **Radical prostatectomy**
 - **Radiotherapy**
 - External Beam (⁺ androgen suppression)
 - Brachytherapy
 - **Watchful waiting**
 - most tumours slowly growing: 10 year rule
 - 25% of patients with clinically localized tumours already have occult metastases ⁷
 - **HIFU [high intensity focused ultrasound]** – no established indication at present: limited to clinical trial settings. Unwanted consequences of HIFU vary considerably with impotence rates 44%-61%, grade 2-3 incontinence 0%-14%, and rectal fistulae 0.7%-3.2% ⁸⁶
 - **Cryotherapy** – no established indication presently: use limited to a clinical trial setting: its most appropriate application is for patients with bulky local disease & local recurrence after radiotherapy rather than as a primary treatment ^{87, 88}
 - **Androgen suppression (palliative)**
-

8. Pre-treatment decision making ²⁰

(a) **Decision-making distress is common** – see Appendix 6, for some web addresses of peer support programmes

- Clinician recommendations strongly influence patient decisions ⁸⁹⁻⁹⁴
- Lay health beliefs also a strong influence ⁹⁵⁻⁹⁷
- A minority (13%) made their decision by weighing up risks & benefits of each treatment option ⁹³

(b) **What is reported to determine the form of treatment**

- Treatment mostly decided by patient's age & urologists' surgical experience in Netherlands ⁹⁸
- For North American men, a younger age, high cancer stage, PSA level & non-African back-ground were associated with receiving treatment with curative intent ⁹⁹
- Men with normal sexual function were more likely to receive watchful waiting & those with normal urinary function were more likely to receive radical prostatectomy ⁹⁹
- The administration of androgen suppression before radical prostatectomy has not resulted in reductions in disease relapse or survival benefit ¹⁰⁰⁻¹⁰³

(c) **Timing of commencement of therapy**

- Not uncommon to wait at least 6 weeks to allow inflammation associated with TRUS biopsies to settle
 - A treatment delay of a few months did not affect recurrence rates ¹⁰⁴
 - Time from TRUS biopsies up to 1 year did not influence probability of biochemical recurrence even in those considered as high risk ¹⁰⁵
-

9. Complications of radical prostatectomy

(a) Peri-operative

- Bleeding – 600-1200 ml not common
- Infection – wound & urinary
- Rectal injuries <1%: Ureteric injuries are rare
- Cardiovascular & respiratory events
- Deep venous thrombosis & pulmonary embolus in ~1% 106-109

(b) Subsequently

- Incontinence: patient-reported satisfactory continence rates in >90% at 12 months ¹¹⁰⁻¹¹⁷
- Bladder neck contracture in <10% 108, 118
- Sexual dysfunction 20
 - Erectile dysfunction is common*
 - Penile shortening 119
 - Loss of libido
 - Less satisfying & painful orgasms 120, 121

Appendix 7 - internet sites for information on prostate cancer & sexuality

10. Sexual function in older men in relation to radical prostatectomy

(a) Sexual function is important in middle aged & older men

- Potency for 435 randomly selected Swedish men aged 50-59, 60-69 & 70-80 years reported to be 97%, 76% and 51%, respectively ¹²²
- Above findings were confirmed in data from 1688 men with a prevalence of significant dysfunction ranging from 3% in 50-54 year olds to 26% in males between 70-78 years ¹²³
- Singer et al (2001) reported that men undergoing treatment for prostate cancer were willing to exchange an approximate 20% chance of being cured of their cancers for an increased prospect of remaining potent after treatment ¹²⁴

(b) Potency rates cited & definitions used vary following nerve-sparing surgery

- If both neurovascular bundles are preserved, reported rates of potency (defined as the ability to sustain sufficient erections for sexual intercourse without any aids other than phosphodiesterase inhibitors) can be as high as 68- 86% ^{125, 126}
 - When only one bundle is saved, reported potency rates diminish substantially ¹²⁷
 - Relapse from +ve surgical margins postero-laterally is uncommon ¹²⁸
 - Radical prostatectomy specimens from men with prostate tumours highly suspicious for posterolateral involvement after excision of the neurovascular bundles on the suspect side, revealed cancer in the neurovascular bundles in only 17.5% ¹²⁷
 - Rosen (1992) confirmed these findings in 144 radical prostatectomy specimens by demonstrating that, when positive margins were present, <10% had involvement in the region of the neurovascular bundles ¹²⁹
-

11. Prediction of recurrence following radical prostatectomy

(a) Information from radical prostatectomy specimen

- **Ten year progression free-rates correlate with grade**

Progression-free rates of

- ~85% for low grade tumours
- ~70% for moderate grade tumours
- ~50% for high grade tumours ¹³⁰⁻¹³⁴

- **Positive margins**

whether surgically-induced or due to extension of the tumour - are associated with ~ a two-fold higher risk of recurrence

~80% 5-year progression-free probability for negative margins 41-64%
5-year progression-free probability for positive margins ^{126, 135}

- **Survival rates decrease with increasing pathological stage**

81% for pT2 tumours
76% for pT3 tumours
19% for N(+) disease ¹³³

9% 7-year disease-free survival for N(+) disease ¹²⁶
26% 7-year disease-free survival for seminal vesicle involvement ¹²⁶

(b) Information from post-operative PSA

- **Common practice to regard a PSA ≥ 0.2 ng/ml as evidence of biochemical recurrence/escape/failure (BE/BR/BF)**

Amling et al (2001) recommended a PSA cut-point of ≥ 0.04 ng/ml to define failure - a lower PSA did not continue to increase in a significant number of patients and these men did not develop demonstrable metastases ¹³⁶

For a PSA of 0.11 to 0.2 ng/ml, the 1 & 3 year risk of PSA progression was 64% & 93%, respectively ¹³⁷ (Freedland et al, 2003)

For a PSA of 0.21 to 0.3 ng/ml, the 1 & 3 year risk of PSA progression was 86% & 100%, respectively ¹³⁷ (Freedland et al, 2003)

Pound et al (1999) reporting on 304 men with biochemical escape (PSA > 0.2 ng/ml following radical prostatectomy, 103 of whom progressed to metastatic disease without having androgen suppression:

Median actuarial time to metastases after BF=8 years
Median actuarial time to death from metastases = 5 years ¹³⁸

- **PSA doubling time is considered a better indicator of outcome**

PSA doubling time <1 year = high risk of dying of prostate cancer within 10 years of diagnosis ¹³⁹

PSA doubling time <3 months met criteria of surrogacy in predicting death from prostate cancer following radical prostatectomy and radiation therapy at a median survival time of 6 years ¹⁴⁰

- (c) **Kattan nomogram for predicting the 10 year progression-free probability after radical prostatectomy**

<http://www.mskcc.org/mskcc/html/10088.cfm> : see Appendix 5

12. Treatment of disease recurrence following radical prostatectomy

(a) Adjuvant radiotherapy – given immediately after surgery to those at significant risk of having residual disease

- **EORTC 22911 trial** ¹⁴¹

Pathologically involved surgical margins or pT3 disease
Randomised 1005 to observation or post-operative radiotherapy
Median follow-up of 5 years

Biochemical progression-free survival of 52.6% versus 74%, respectively
Clinical progression & loco-regional failure rates also significantly improved
Grade 3 toxicity was uncommon
urinary incontinence rate not increased ¹⁴²

- **German Cancer Society (ARO 96-02 / AUO AP 0995)** ¹⁴³

Positive margins or pT3 & undetectable PSA post-prostatectomy
Median follow-up of 3 years for 261 patients

>20% improvement in biochemical failure rate for radiotherapy arm
Absence of grade 3 rectal toxicity

- **SWOG 8794** ¹⁴⁴

Randomised 419 pT3 & margin +ve men to observation or radiotherapy
55% had a detectable PSA post-prostatectomy

Risk of Biochemical recurrence was reduced by 56% with radiotherapy
No significant differences in G-I and Urinary tract QoL domains at 5 years

- **Thompson et al 2006**

425 men with pathologically advanced prostate cancer who had undergone radical prostatectomy (i.e. stage pT3 N0 M0) were randomly assigned to receive 60 to 64 Gy of external beam radiotherapy delivered to the prostatic fossa (n = 214) or usual care plus observation (n = 211).

The median follow-up was 10.6 years (interquartile range, 9.2-12.7 years). For metastasis-free survival, 76 (35.5%) of 214 men in the adjuvant radiotherapy group were diagnosed with metastatic disease or died (median metastasis-free estimate, 14.7 years), compared with 91 (43.1%) of 211 (median metastasis-free estimate, 13.2 years) of those in the observation group (P = .06).

There were no significant between-group differences for overall survival (71 deaths, median survival of 14.7 years for radiotherapy vs 83 deaths,

median survival of 13.8 years for observation (P = .16). Median PSA relapse-free survival was 10.3 years for radiotherapy vs 3.1 years for observation (P<.001) and the median recurrence-free survival was 13.8 years for radiotherapy vs 9.9 years for observation (P = .001).

Adverse effects were more common with radiotherapy vs observation (23.8% vs 11.9%), including rectal complications (3.3% vs 0%), urethral strictures (17.8% vs 9.5%), and total urinary incontinence (6.5% vs 2.8%).

Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, Messing E, Forman J, Chin J, Swanson G, Canby-Hagino E, Crawford ED. JAMA, 2006;296(19):2329-35

(b) Salvage radiotherapy – conducted when recurrence is expected such as a PSA rise post-prostatectomy

- Unlike adjuvant radiotherapy, there are no prospective studies of efficacy or toxicity to guide decisions
 - Retrospective analyses suggest PSA level prior to salvage radiotherapy is strongly predictive of outcome ¹⁴⁵⁻¹⁴⁷
 - Suggestions that patients with PSA levels <1 ng/ml at commencement of treatment do better¹⁴⁸ & that this is independent of PSA doubling time ¹⁴⁹
 - Larger series show a biochemical control rate of ~50% ^{147, 150} with >70% with a pre-treatment PSA <1 ng/ml & an operative Gleason score of 7 or lower ¹⁴⁸
-

13. Stratification of patients for Radiotherapy with curative intent ²⁰

- **Low risk:** PSA≤10 ng/mL and Gleason Score 2-6 and stage cT1-cT2a
 - **High risk:** either cT3 or cT4 or PSA>20 ng/mL or Gleason Score 8-10
 - **Intermediate risk** falls between these levels
-

14. External Beam Radiotherapy

(a) Low-risk prostate cancer

- PSA control in >85% using conformal or intensity modulated techniques

(b) High-risk prostate cancer

- External Beam radiotherapy plus androgen suppression for 2 years ¹⁵¹ 3 years ¹⁵² or indefinitely, improves results for locally advanced tumours
- An overall survival benefit of 16% at 5 years was reported for the combination of androgen suppression plus external beam in comparison with external beam therapy alone ¹⁵²

(c) Intermediate-risk prostate cancer

- Lesser need to address sub-clinical metastatic disease at diagnosis
- Dose-escalation advocated ^{151, 153, 154}
- For patients with PSA 10-20 ng/ml, the freedom from failure at 6 years increased from 43% to 62% in a randomized trial when the dose was increased from 70 Gy to 78 Gy ¹⁵⁵
- Short-term androgen suppression combined with external beam radiotherapy has shown to be of benefit to some patients - **Appendix 8**

(d) Toxicity

- **Urinary symptoms**

Symptomatic but not requiring medical intervention in approximately 50%

Serious problems <1%

Urethral strictures 1% ¹⁶⁰

- **Rectal symptoms**

Urgency & frequency present for most men towards the course of therapy

A measurable but not clinically problematic change in bowel habit 10-20%

Rectal bleeding during or soon after treatment in 0-2% Late bleeding rate of approximately 1% ¹⁶⁰

Most bowel dysfunction settles over 1-2 years then remains stable ¹⁶¹

- **Erectile dysfunction**

For those with adequate erections prior to radiotherapy, approximately 50% will maintain erectile function for 1 ¹⁶² or more than 2 years ¹⁶³

Sexual function deteriorated over time in all series studied ¹⁶¹

To be expected during androgen suppression

15. Brachytherapy

(a) Low-dose rate (LDR) permanent radioactive seed implant

metal seeds, containing Iodine ¹²⁵ or Palladium ¹⁰³ as the radioactive source

Outpatient setting

- **Efficacy**

Although few published long-term results are beyond 10 years, tumour control rates appear to be similar to those of surgery ^{164, 165}

Biochemical control rates for patients in the low-risk group >85%: high-risk patients have a poor outlook with LDR brachytherapy alone ^{164, 166-168}

No randomised evidence for brachytherapy with androgen suppression or external beam radiotherapy ¹⁶⁸

- **Toxicity**

Irritative LUTS are most common, peaking at 2-10 weeks: majority return to baseline at 12 months ¹⁶⁹. However, continence may deteriorate over the next 4 years ¹⁷⁰

Rectal toxicity is uncommon with bleeding or fistula formation occurring in <1% ¹⁷¹

~30-50% lose adequate erectile function by 3 years ¹⁷²⁻¹⁷⁸

(b) HDR temporary implant

- **Efficacy**

Used in a number of centres for well over a decade ¹⁷²⁻¹⁷⁸

Series routinely report freedom from biochemical failure results >90% and >90% and >80% for low and intermediate-risk patients, respectively ^{174, 176, 177}

- **Toxicity**

Severe late (grade 3) urinary symptoms occur in ~5%

Significant rectal toxicity is uncommon

Erectile dysfunction is poorly reported to date ²⁰

16. Treatment of suspected local recurrence following radiotherapy ²⁰

Optimal candidate for *local-only* salvage therapy defined as one whose pre-treatment PSA velocity was <2 ng/ml/year, interval to PSA failure exceeded 3 years, post-treatment PSA doubling time was at least 12 months and whose TRUS biopsy cores contained a Gleason score <8 ¹⁷⁹

Options

- **Salvage radical prostatectomy**

Projected and reported biochemical relapse-free rates of 55-69% at 5 years but with higher rectal injury, bladder neck contracture & urinary incontinence rates ¹⁸⁰

- **Cryotherapy**

Its most appropriate application is for bulky local disease and local recurrence after radiation therapy: experience is presently limited to a few academic centres: toxicity data is limited ^{87, 88, 180}

- **High-Intensity Focused Ultrasound (HIFU)**

Current experience is too limited to recommend ⁸⁶

- **Androgen suppression therapy**

17. Androgen suppression therapy for metastatic disease

- Approximately 25% treated initially with curative intent experience PSA failure or develop clinically detectable metastases within 5 years ¹⁸¹
 - A considerable proportion of patients continue to present with extra-prostatic disease ¹⁸²
 - Approximately 80% of patients have a durable clinical regression with androgen suppression therapy
 - The median time to relapse is 18 months ¹⁸³
 - The American Society of Clinical Oncology recommends bilateral orchidectomy or LHRH agonists as initial androgen suppression treatments ¹⁸⁴
 - Non-steroidal anti-androgens may be considered alternatives but the steroidal anti-androgen cyproterone acetate should not be recommended as primary monotherapy, particularly because of the risk of hepatotoxicity ¹⁸⁴
-

18. Timing of commencement of androgen suppression therapy

Points for consideration

- **There is a lack of compelling evidence that commencing androgen suppression early improves survival** [102](#), [103](#), [184-188](#) (Appendix 9 p28, 29)
- **However, early commencement does increase the likelihood & duration of side effects which impact upon lifestyle**

- Loss of libido
- Impotence
- Reduction in mobility via osteoporosis & loss of muscle mass
- Change in body habitus
- Adverse cognitive changes in ~50% [189](#)
- Impaired liver function (for anti-androgens)

- **A body of clinicians advocates carefully delaying commencement by balancing the unwanted effects of treatment with those of the disease being treated, in conjunction with**

- patients' wishes
- PSA doubling time
- Development of lesions on bone scans

In patients with non-localised prostate cancer, Green et al (2004) reported in a randomised controlled study, more instances of a deterioration of quality of life for the men on hormonal treatments at 12 months, in particular in relation to sexual function, compared with men randomised to watchful waiting [189](#)

- **Androgen suppression reduces the de-differentiating influence on prostate cancer cells via ER β** [20](#), [190-192](#)
- **However, androgen suppression therapy effectively lowers serum PSA (albeit temporarily) in the large majority of patients addressing the pre-occupation of many patients and clinicians**

A 2001 survey of American Urologists indicated that 68% recommended hormone suppression therapy for an elevated PSA after radical prostatectomy [193](#)

- **Hot flushes**

Common especially following LHRH administration or bilateral orchidectomy: can be managed by low-dose cyproterone acetate, oestrogen or transdermal oestrogen (see 19c)

19. Forms of androgen suppression therapy 194, 195

(a) Common side effects of androgen suppression treatments

	Bilateral Orchidectomy	LHRH agonists	Anti-androgens
Flare reaction		+	
Reduced libido	+	+	+
Impotence	+	+	+
Hot flushes	+	+	+
Sweating		+	+
Cognitive changes	+	+	+
Osteoporosis	+	+	
Loss of muscle mass	+	+	
BP changes		+	
Anaemia	+	+	
Gynaecomastia		+	+
Breast discomfort			+
Arthralgia		+	
Myalgia		+	
Dyspnoea		+	+
Peripheral oedema		+	
Dizziness		+	
Nausea/vomiting		+	+
Impaired LFTs			+
Headache		+	+
Depression			+
Insomnia			+
Lethargy			+
Skin reactions		+	+
Body hair loss			+

(b) Further anti-androgen toxicities

- Hepatic failure is rare but can be fatal with cyproterone acetate
- Nilutamide is associated with alcohol intolerance, impaired adaptation to darkness & interstitial pneumonitis
- Diarrhoea is more common with flutamide than bicalutamide, infrequent with cyproterone acetate and does not occur with nilutamide

(c) Oestrogen therapy

Rarely used because of cardiovascular complications associated with oral administration. However, a low-dose of stilboestrol at 1 mg daily (with or without aspirin) stated to be comparable with bilateral orchidectomy in the treatment of advanced disease without the increased risk of cardiovascular complications

However, cardiovascular complications are significantly reduced or avoided by parenteral delivery via injected depot or transdermal patch [196, 197](#)

Considered not to induce osteoporosis and may improve bone density [198-200](#)

Oestrogens are cheap and may have a role in ameliorating agitation in some men receiving LHRH agonists [199](#)

(d) Intermittent androgen blockade (IAB)

Usually limited to those patients who demonstrate a pronounced PSA response and who find the effects of androgen suppression problematical

However, not all the adverse effects of androgen suppression are reversible

Castrate levels of testosterone may persist for up to 1 year and longer after cessation of LHRH agonists [201](#)

(e) Combined androgen blockade

Only a modest survival benefit has been demonstrated for combined androgen blockade compared with monotherapy - but at the cost of a higher side-effect profiles for patients [202](#)

The limited survival benefit with the use of non-steroidal anti-androgens and only becomes evident after 5 years of therapy [184](#)

20. Hormone escape

(a) Life expectancy (Newling et al,1993) ^{203*}

Median time for survival following PSA progression was

- PSA progression was 52 weeks
- Bone metastases was 41 weeks
- Regional & distant lymph nodes was 28 & 33 weeks, respectively

**** May understate current status because of significant reductions in PCa mortality over the past decade or so in many western countries ³***

Life expectancy (Smith et al, 2005)

201 patients with non-metastatic PCa with rising PSA At 2 years

- 33% had developed bone metastases
- Median bone-metastasis-free survival was 30 months
- Median time to first bone metastases & overall survival were not reached
- Baseline PSA >10 ng/ml & PSA velocity independently predicted shorter time to first bone metastases
- Baseline PSA & PSA velocity also independently predicted overall survival & metastasis-free survival

Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, Wynne C, Murray R, Zinner NR, Schulman C, Linnartz R, Zheng M, Goessl C, Hei YJ, Small EJ, Cook R, Higano CS. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol, 2005; 23(13):2918-25.

(b) Androgen suppression needs to be continued but reviewed

With hormone escape, there is amplification and over-expression of the androgen receptor (**AR**) gene, as well as post-translational modifications to the AR so that the cancer cells become 'super-sensitive' to androgens ²⁰⁴⁻²⁰⁶

At this stage, a variety of ligands including hormones and drugs, especially anti-androgens, may become mitogens. Changing the form of androgen suppression may be beneficial clinically, albeit temporarily ^{207, 208}

Second-line hormone treatments: addition of an anti-androgen to patients receiving monotherapy via an LHRH agonist or bilateral orchidectomy may be beneficial for a short time. There may also be a place for oestrogen therapy (either alone or as estramustine) at this stage ²⁰⁹. Other treatments used include corticosteroids and, less commonly, aminoglutethamide.

(c) Urological considerations at this stage (Clarke et al, 2003) ²¹⁰

- Lower urinary tract dysfunction
- Ureteric obstruction
- Skeletal, dysfunction
- Bone marrow insufficiency
- Lymphoedema
- Rectal obstruction/infiltration
- Pain
- Psychological dysfunction/impaired quality of life

(d) Bisphosphonates

- **Mode of introduction**

Initially they were examined for prophylaxis & treatment of osteoporosis in women²¹⁰ but, more recently, in men following androgen deprivation +/- external beam radiotherapy 210, 212

Act by inhibiting osteoclast activity 213

- **Clinical evidence**

The third generation bisphosphonate, zoledronic acid, demonstrated increased apoptosis in prostate cancer cell lines *in vitro* and inhibited growth of osteoblastic and osteolytic metastases *in vivo* 214, 215

Saad et al (2004) reported a median time to the first skeletal related event of 488 days for patients receiving 4-mg zoledronic acid group compared with 321 days for a placebo group & concluded that, compared with placebo, zoledronic acid reduced the ongoing risk of skeletal related events by 36% 216

- **Common adverse events with IV Zoledronate administration**

- Fever
- Flu-like symptoms
- Injection site reaction
- Myalgia & arthralgia
- Bone pain
- Headaches
- Conjunctivitis
- GI symptoms
- Hypertension
- Increased creatinine concentration
- Hypophosphataemia
- hypocalcaemia

(e) Chemotherapy

- **Mitoxantrone**

Mitoxantrone and prednisone reduced analgesic requirements & for a sustained period (Tannock et al, 1996) ²¹⁷

Mitoxantrone and hydrocortisone improved QoL but not survival (Kantoff et al, 1999) ²¹⁸

- **Docetaxel (Appendix 10)**

Acts by blocking the ability of cells to depolymerize the microtubule cytoskeleton during normal mitosis

Used as single agent therapy, docetaxel showed significant PSA responses (a PSA level decline of greater than 50%) in 38-48%, and up to 68% in early phase combination therapy trials ²¹⁹

Recent studies have shown a median survival benefit of 2-2.5 months ^{220, 221}

- **Common adverse events with Mitoxantrone & Docetaxel** ^{194, 195}

	Mitoxantrone	Docetaxel
Myelosuppression	+	+
Lassitude	+	+
Stomatitis	+	
Oesophagitis	+	
Nausea & vomiting	+	+
Alopecia	+	+
Blue-green urine	+	
Hypersensitivity reactions		+
Fluid retention (ascites, Pleural effusions, oedema)		+
Rash		+
Dry eyes		+

(f) Bone-seeking radio-isotopes ²²¹⁻²²⁸

- Strontium ⁸⁹ & Samarium ¹⁵³
- Strontium ⁸⁹ (Sr⁸⁹) is a pure β emitter, with a t_{1/2} ~50 days
- Samarium ¹⁵³ is chelated to EDTMP to enhance binding to bone
- Samarium ¹⁵³ is a β and γ emitter & has a t_{1/2} ~46 hrs
- Neither agent has much effect on non-bony tissues

- Maximal effect on pain is usually seen in 2-4 weeks
 - both typically reducing pain to some degree in 70% of patients
 - Analgesic effect lasts for 3-4 months on average
 - Bone marrow suppression is the major toxicity
-

APPENDIX 1: WHETHER OR NOT TO DIAGNOSE

1a How Clinicians Can Help Men Make Decisions about Treatment

Effective decision making is when a person makes a health care decision that is:

- informed and consistent with their values and preferences
- when the person is involved in the decision to the extent that they prefer
- when the person has adequate and appropriate support

1b Tips for helping patients

- provide good quality written information about options
- identify most salient points for the patient to consider
- when possible have a support person present for consultations
- communicate risk effectively (**see 1d**)
- give the patient time to consider and ask questions
- suggest the patient write up a list of pros and cons for different treatment options for discussion with you and significant others (**see 1e**)
- ensure the patient has contacts for support and information: Cancer Helpline, Lions prostate health website, peer support groups
- offer a second opinion if needed

1c

Six Decision Steps for making an Informed Choice about PSA Testing in Asymptomatic Men

1. Identify the patient's main concern
2. Explain where the prostate is and tests available to detect prostate cancer
3. Discuss prostate cancer risk and risk factors
4. Explain the pros and cons of early detection of prostate cancer
5. Identify patient's personal preferences
6. Support the patient's choice, and if requested implement a prostate cancer risk management plan (**FTU**)

1d

Communication strategies suggested to help patients understand risk include

1. Use numbers as well as words to explain risk
2. Where possible provide the absolute risk or benefit
3. Use frequencies rather than single event probabilities
4. Use consistent denominators
5. Put the risk into context by comparing it to other life events
6. Offer both the possible negative and positive outcomes to balance the message frame. (Refs [19-22](#))

1e Determining what is most important for each individual patient

<u>FOR: Is this like you?</u>	<u>AGAINST: Is this like you?</u>
I'm concerned that I might get prostate cancer	I think my chance of getting prostate cancer is low
I want the best chance of finding it Early, if I do get it	I am not convinced about the effectiveness of testing
I'm not interested in waiting for all the proof to be in	I am more concerned about avoiding treatment side effects, if there's no guarantee I'd be reducing my risk of dying from prostate cancer
I want to do everything possible to reduce my risk of dying from prostate cancer	

APPENDIX 2: AGE-RELATED PSA LEVELS

AGE-BASED RANGES FOR PSA FOR WESTERN MEN

Age range	50 th percentile (median)	95 th percentile (upper limit of normal)
40-49	0.65	2.0
50-59	0.85	3.0
60-69	1.39	4.0
70-79	1.64	5.5

- Between 50th & 95th percentile, higher long-term risk of cancer
- PSA increases at ~3.3% pa – if rate of increase is greater, the risk of cancer is greater

Oesterling et al, 1995; Fang et al, 2001; Gann et al, 1995; Carter et al, 1992

2(a) Age-based PSA ranges for men in western societies (Refs: 20-24)

AGE-BASED 95TH PERCENTILE FOR PSA FOR JAPANESE MEN

Age range	Imai 1994	Imai 1995	Oesterling	Ito
40-49	1.33	2.1	2.0	
50-59	3.65	2.9	3.0	
60-69	4.06	4.0	4.0	3.0/3.5
70-79	5.09	5.2	5.0	4.0
80-89	5.66	5.9		7.0

Ku (2006) citing Imai et al, 1994 & 1995; Oesterling et al, 1995; Ito et al, 2000

2 (b) Age-based PSA ranges for Japanese men (Refs: 25-28)

AGE-BASED 95TH PERCENTILES FOR PSA IN CHINESE MEN

Age range	PSA in ng/ml
20-29	1.20
30-39	1.21
40-49	1.23
50-59	2.35
60-69	3.20
70-79	3.39
80-89	3.39

Ku (2006) citing He et al, 2004

2 (c) Age-based PSA ranges for Chinese Men (Refs: [25](#), [29](#))

AGE-BASED 95TH PERCENTILE FOR PSA FOR TAIWANESE MEN

Age range	95 th Percentile (ng/ml)		
	Lin	Kao	Wu
20-29	1.92	1.50	
30-39	1.85	1.50	
40-49	2.59	1.88	
50-59	3.31	2.37	4.0
60-69	5.03	4.82	6.0
70-79	5.73	5.96	5.0

Ku (2006) citing Lin et al, 1996; Kao, 1997; Wu & Huang, 2004

2 (d) Age-based PSA ranges for Taiwanese men (Refs: [25](#), [30-32](#))

AGE-BASED 95TH PERCENTILE FOR PSA FOR SINGAPOREAN MEN

Age range	Tay	Saw
30-39		1.4
40-49		1.7
50-59	3.51	2.3
60-69	3.78	4.0
70-79	6.02	6.3
80-89	6.02	6.6

Ku (2006) citing Tay et al, 1996; Saw & Aw, 2000

2 (e) Age-based PSA ranges for Singaporean men (Refs: [25](#), [33](#), [34](#))

AGE-BASED 95TH PERCENTILE FOR PSA FOR KOREAN MEN

	Age range	
	Lee	Ku
20-29		2.25
30-39	1.8	2.35
40-49	2.0	2.36
50-59	2.5	2.96
60-69	3.9	3.78
70-79	5.8	7.49

Ku (2006) citing Lee et al, 2000; Ku et al, 2002

2 (f) Age-based PSA ranges for Korean men (Refs: [25](#), [35](#), [36](#))

APPENDIX 3: CRITERIA FOR GLEASON GRADING

Gleason grading system		
Grade	Histology	Biologic Behaviour
1 & 2	closely-packed glands forming a nodule	Indolent disease, rarely progressive
3	small infiltrating glands, complete lumen formation	most common pattern; less aggressive than pattern 4
4	fused glands, incomplete lumen formation	indicates tumour progression
5	solid sheet or single cells, no lumen formation	Very aggressive, late stage

APPENDIX 4: PARTIN TABLES FOR PREDICTING PATHOLOGICAL STAGE

TABLE 1. Clinical Stage T1c (nonpalpable, PSA elevated)

PSA Range (ng/mL)	Pathology Stage	Gleason Score				
		2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10
0-2.5	Organ confined	95 (89-99)	90 (88-93)	79 (74-85)	71 (62-79)	66 (54-76)
	Extraprostatic extension	5 (1-11)	9 (7-12)	17 (13-23)	25 (18-34)	28 (20-38)
	Seminal vesicle (+)	—	0(0-1)	2 (1-5)	2(1-5)	4 (1-10)
	Lymph node (+)	—	—	1 (0-2)	1 (0-4)	1 (0-4)
2.6-4.0	Organ confined	92 (82-98)	84 (81-86)	68 (62-74)	58 (48-67)	52 (41-63)
	Extraprostatic extension	8 (2-18)	15 (13-18)	27 (22-33)	37 (29-46)	40 (31-50)
	Seminal vesicle (+)	—	1 (0-1)	4 (2-7)	4 (1-7)	6 (3-12)
	Lymph node (+)	—	—	1 (0-2)	1(0-3)	1 (0-4)
4.1-6.0	Organ confined	90 (78-98)	80(78-83)	63 (58-68)	52 (43-60)	46 (36 - 56)
	Extraprostatic extension	10 (2-22)	19 (16-21)	32 (27-36)	42 (35-50)	45 (36-54)
	Seminal vesicle (+)	—	1 (0-1)	3 (2-5)	3 (1-6)	5 (3-9)
	Lymph node (+)	—	0 (0-1)	2 (1-3)	3 (1-5)	3 (1-6)
6.1-10.0	Organ confined	87 (73-97)	75 (72-77)	54 (49-59)	43 (35-51)	37 (28-46)
	Extraprostatic extension	13 (3-27)	23 (21-25)	36 (32-40)	47 (40-54)	48 (39-57)
	Seminal vesicle (+)	—	2 (2-3)	8 (6-11)	8 (4-12)	13 (8-19)
	Lymph node (+)	—	0 (0-1)	2 (1-3)	2 (1-4)	3 (1-5)
>10.0	Organ confined	80 (61-95)	62 (58 -64)	37 (21-34)	27 (21-34)	22 (16-30)
	Extraprostatic extension	20 (5-39)	33 (30-36)	43 (38-48)	51(44-59)	50 (42-59)
	Seminal vesicle (+)	—	4 (3-5)	12 (9-17)	11(6-17)	17 (10-25)
	Lymph node (+)	—	2 (1-3)	8(5-11)	10 (5-17)	11 (5-18)

KEY: PSA = prostate-specific antigen

TABLE II. Clinical Stage T2a (palpable, < 1/2 of one lobe)

PSA Range (ng/mL)	Pathology Stage	Gleason Score				
		2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10
0-2.5	Organ confined	91 (79-98)	81 (77-85)	64 (56-71)	53 (43-63)	47 (35-59)
	Extraprostatic extension	9 (2-21)	17 (13-21)	29 (23-26)	40(30-49)	42 (32-53)
	Seminal vesicle (+)	—	1 (0-2)	5 (1-9)	4 (1-9)	7 (2-16)
	Lymph node (+)	—	0 (0-1)	2 (0-5)	3 (0-8)	3 (0-9)
2.6-4.0	Organ confined	85 (69-96)	71 (66-75)	50 (43-57)	39 (30-48)	33 (24-44)
	Extraprostatic extension	15 (4-31)	27 (23-31)	41 (35-48)	52 (43-61)	53 (44-63)
	Seminal vesicle (+)	—	2(1-3)	7 (3-12)	6 (2-12)	10 (4-18)
	Lymph node (+)	—	0 (0-1)	2 (0-4)	2 (0-6)	3 (0-8)
4.1-6.0	Organ confined	81 (63-95)	66 (62-70)	44 (39-50)	33 (25-41)	28 (20-37)
	Extraprostatic extension	19 (5-37)	32 (28-36)	46 (40-52)	56 (48-64)	58 (49 - 66)
	Seminal vesicle (+)	—	1 (1-2)	5 (3-8)	5 (2-8)	8 (4-13)
	Lymph node (+)	—	1(0-2)	4 (2-7)	6 (3-11)	6 (2-12)
6.1-10.0	Organ confined	76 (56-94)	58 (54-61)	35 (30-40)	25 (19-32)	21 (15-28)
	Extraprostatic extension	24 (6-44)	37 (34-41)	49 (43-54)	58 (51-66)	57 (48-65)
	Seminal vesicle (+)	—	4 (3-5)	13 (9-18)	11 (6-17)	17 (11-26)
	Lymph node (+)	—	1 (0-2)	3 (2-6)	5 (2-8)	5 (2-10)
>10.0	Organ confined	65 (43-89)	42 (38-46)	20 (17-24)	14 (10-18)	11 (7-15)
	Extraprostatic extension	35 (11-57)	47 (43-52)	49 (43-55)	55 (46-64)	52 (41-62)
	Seminal vesicle (+)	—	6 (4-8)	16 (11-22)	13 (7-20)	19(12-29)
	Lymph node (+)	—	4 (3-7)	14 (9-21)	18 (18-27)	17 (9-29)

KEY: PSA = prostate-specific antigen

TABLE III. Clinical Stage T2b (palpable, < 1/2 of one lobe, not on both lobes)

PSA Range (ng/mL)	Pathology Stage	Gleason Score				
		2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10
0-2.5	Organ confined	88 (73-97)	75 (69-81)	54 (46-63)	43 (33-54)	37 (26-49)
	Extraprostatic extension	12 (3-27)	22 (17-28)	35 (28-43)	45 (35-56)	46 (35-58)
	Seminal vesicle (+)	—	2 (0-3)	6 (2-12)	5 (1-11)	9 (2-20)
	Lymph node (+)	—	1 (0-2)	4 (0-10)	6 (0-14)	6 (0-16)
2.6-4.0	Organ confined	80 (61-95)	63 (57-69)	41 (33-48)	30 (22-39)	25 (17-34)
	Extraprostatic extension	20 (5-39)	34 (28-40)	47 (40-55)	57 (47-67)	57 (46-68)
	Seminal vesicle (+)	—	2 (1-4)	9 (4-15)	7 (3-14)	12 (5-22)
	Lymph node (+)	—	1 (0-2)	3 (0-8)	4 (0-12)	5 (0-14)
4.1-6.0	Organ confined	75 (55-93)	57 (52-63)	35 (29-40)	25 (18-32)	21 (14-29)
	Extraprostatic extension	25 (7-45)	39 (33-44)	51(44-57)	60 (50-68)	59 (49-69)
	Seminal vesicle (+)	—	2 (1-3)	7 (4-11)	5(3-9)	9 (4-16)
	Lymph node (+)	—	2 (1-3)	7(4-13)	10 (5-18)	10 (4-20)
6.1-10.0	Organ confined	69 (47-91)	49 (43-54)	26 (22-31)	19 (14-25)	15 (10-21)
	Extraprostatic extension	31 (9-53)	44 (39-49)	52 (46-58)	60 (52-68)	57 (48-67)
	Seminal vesicle (+)	—	5 (3-8)	16 (10-22)	13 (7-20)	19 (11-29)
	Lymph node (+)	—	2 (1-3)	6 (4-10)	8 (5-14)	8 (4-16)
>10.0	Organ confined	57 (35-86)	33 (28-38)	14 (11-17)	9 (6-13)	7 (4-10)
	Extraprostatic extension	43 (14-65)	52 (46-56)	47 (40-53)	50 (40-60)	46 (36-59)
	Seminal vesicle (+)	—	8 (5-11)	17 (12-24)	13 (8-21)	19 (12-29)
	Lymph node (+)	—	8 (5-12)	22 (15-30)	27 (16-39)	27 (14-40)

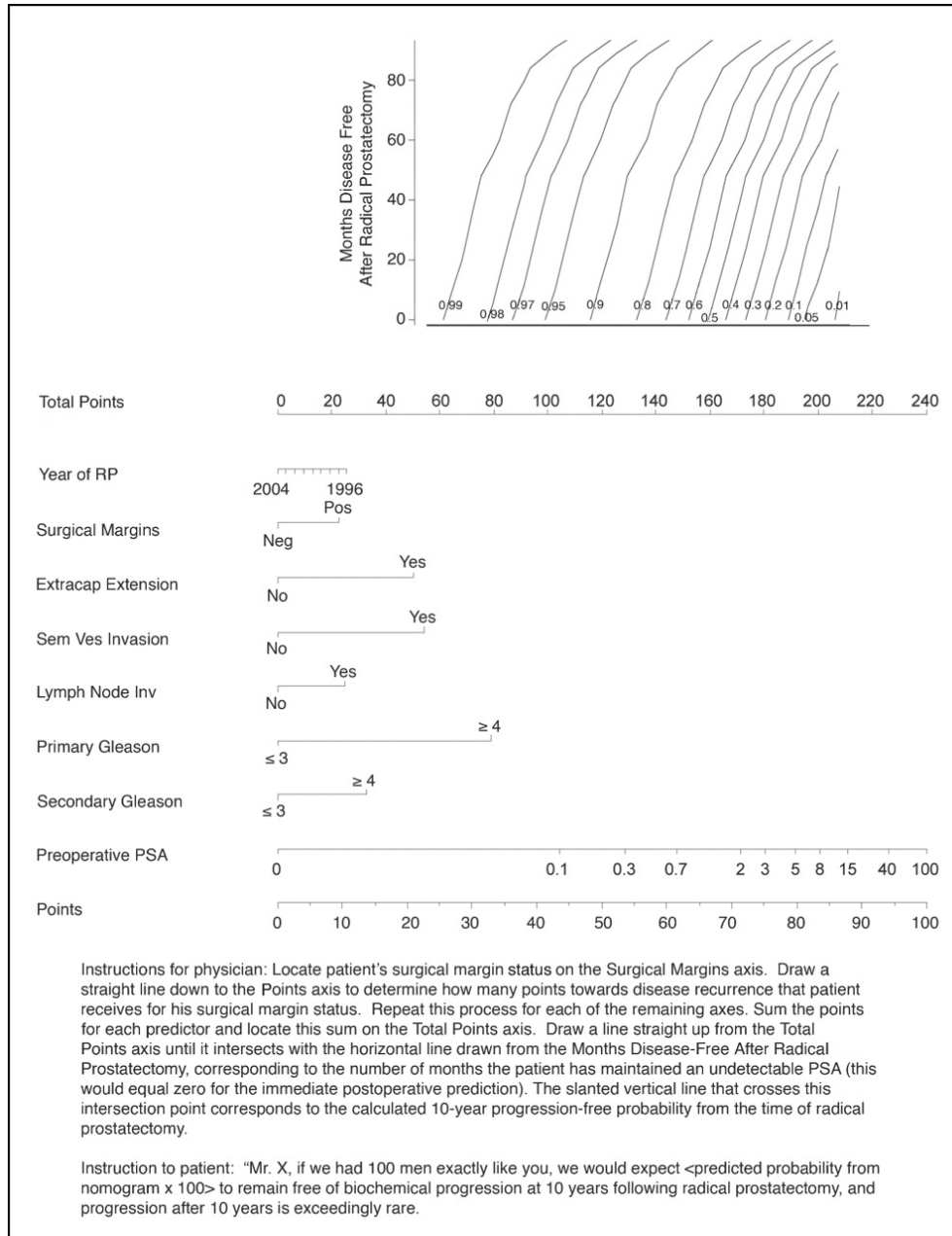
KEY: PSA = prostate-specific antigen

TABLE IV. Clinical Stage T2c (palpable on both lobes)

PSA Range (ng/mL)	Pathology Stage	Gleason Score				
		2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10
0-2.5	Organ confined	81 (71-97)	73 (63-81)	51 (38-63)	39(26-54)	34 (21-48)
	Extraprostatic extension	14 (3-29)	24 (17-33)	36 (26-48)	45 (32-59)	47 (33-61)
	Seminal vesicle (+)	—	1 (0-4)	5 (1-13)	5 (1-12)	8 (2-19)
	Lymph node (+)	—	1 (0-4)	6 (0-18)	9 (0-26)	10(0-27)
2.6-4.0	Organ confined	78 (58-94)	61 (50-70)	38 (27-50)	27 (18-40)	23 (14-34)
	Extraprostatic extension	22 (6-42)	36 (27-45)	48 (37-59)	57 (44-70)	57 (44-70)
	Seminal vesicle (+)	—	2 (1-5)	8 (2-17)	6 (2-16)	10 (3-22)
	Lymph node (+)	—	1 (0-4)	5 (0-15)	7 (0-21)	8 (0-22)
4.1-6.0	Organ confined	73 (52-93)	55 (44-64)	31 (23-41)	21 (14-31)	18 (11-28)
	Extraprostatic extension	27 (7-48)	40 (32-50)	50 (40-60)	57 (43-68)	57 (43-70)
	Seminal vesicle (+)	—	2 (1-4)	6 (2-11)	4 (1-10)	7 (2-15)
	Lymph node (+)	—	3 (1-7)	12 (5-12)	16 (6-32)	16 (6-33)
6.1-10.0	Organ confined	67 (45-91)	46 (36-56)	24 (17-32)	16 (10-24)	13 (8-20)
	Extraprostatic extension	33 (9-55)	46 (37-55)	52 (42-61)	58 (46-69)	56 (43-69)
	Seminal vesicle (+)	—	5 (2-9)	13 (6-23)	11 (4-21)	16 (6-29)
	Lymph node (+)	—	3 (1-6)	10(5-18)	13 (6-25)	13(5-26)
>10.0	Organ confined	54 (32-85)	30 (21-38)	11 (7-17)	7(4-12)	6 (3-10)
	Extraprostatic extension	46 (15-68)	51 (42-60)	42 (30-55)	43 (29-59)	41 (27-57)
	Seminal vesicle (+)	—	6 (2-12)	13 (6-24)	10 (3-20)	15 (5-28)
	Lymph node (+)	—	13 (6-22)	33 (18-49)	38 (20-58)	38 (20-59)

KEY: PSA = prostate-specific antigen

APPENDIX 5: KATTAN NOMOGRAM



APPENDIX 6: WEB ADDRESSES FOR SOME PEER SUPPORT PROGRAMMES

Group Example	Website
Canadian prostate cancer Network (CAN)	http://www.cpcn.org/
Us Too (US)	http://www.ustoo.com/
PSA: Prostate cancer Support Association (UK)	http://www.prostatecancersupport.info/
Prostate cancer Foundation of Australia (AUST)	http://www.prostate.org.au/support.htm
Prostate Awareness and Support Society (NZ)	http://www.prostate.org.nz/index.html
The Scottish Association of prostate cancer Support Groups	http://www.prostatescot.co.uk/
Irish Cancer Society: Men against cancer	http://www.cancer.ie/support/mac.php

APPENDIX 7: SOME INTERNET SITES FOR INFORMATION ON PROSTATE CANCER & SEXUALITY**Internet Sites**

Oncolink has links to chatlines for sexuality and cancer or fertility and cancer, and links to other useful sites.

www.oncolink.upenn.edu/psychosocial/sexuality

Cancer Source offers interactive tools and community resources.

www.cancersource.com

Association of Cancer Online Resources is a cancer online information system that offers access to electronic mailing lists and links to other sites.

www.acor.org

Andrology Australia has resources about sexual dysfunction.

www.andrologyaustralia.org

The Lions Prostate cancer Website has information on prostate cancer treatment and support groups, links to other sites, as well as an email advisory service.

www.prostatehealth.org.au

APPENDIX 8: EXTERNAL BEAM RADIOTHERAPY FOR INTERMEDIATE RISK PATIENTS

- The RTOG 86-10 trial showed a benefit for patients randomized to 2 months of complete androgen suppression before and during radiotherapy compared with radiotherapy alone for bulky primary tumours 156
 - Another randomized controlled trial demonstrated freedom from failure together with a survival advantage to having 6 months of neoadjuvant androgen suppression prior to 70Gy of EBRT in intermediate and high risk men 157
 - Trans-Tasman Radiation Oncology Group (TROG) 96.01 trial compared radiotherapy of 66Gy alone with the same dose in combination with either 3 or 6 months of neoadjuvant maximum androgen blockade. A benefit was shown for 6 months androgen suppression in terms of freedom from biochemical failure and cancer-specific mortality primarily for high risk men 158
 - A further trial in which the calculated risk of nodal positivity was >15% showed that 4 months of androgen suppression was a significant benefit only when given prior to and during radiotherapy (rather than adjuvantly), and furthermore, only when combined with whole pelvic radiation fields (rather than prostate only) 20, 159
-

APPENDIX 9: EORTC TRIAL 30891 – IMMEDIATE OR DEFERRED ANDROGEN DEPRIVATION FOR PATIENTS NOT SUITABLE FOR LOCAL TREATMENT WITH CURATIVE INTENT ¹⁸⁸

985 with newly diagnosed T0-T4, N0-2 M0

Inclusion: All either refused local definitive treatment or were judged not suitable due to a decreased life expectancy, advanced tumour stage &/or severe comorbidities

Exclusion: >80 yr; other malignancies; prostate cancer-induced pain or ureteric obstruction; proven juxtaregional metastatic lymph nodes

Randomised to immediate androgen deprivation (492) or deferred commencement indicated by symptomatic progression or serious complications (493)

Androgen suppression = bilateral orchidectomy or buserelin (with 2 weeks of cyproterone acetate)

Symptomatic progression definition: new symptomatic metastases or metastases likely to produce serious complications, increased pain score $\geq 2/4$ categories, deterioration in WHO performance status by 2 levels due to prostate cancer, ureteric obstruction by prostate cancer

1002 recruited but 17 excluded because of problems with source documentation

Deferred group had 14 more cT2 & 19 more Grade 3 tumours compared with other group despite randomisation, other parameters being comparable

Immediate group**Deferred group**

12/492 = ineligible = 13/493

17/480 (29/492) = not treated as per protocol = 43/480 (56/493)

475/492 = treated by androgen suppression as per protocol = 245/493*

(* 125 died without needing treatment: 80 alive without indication for treatment
Median time from study entry to treatment initiation for deferred group was 7 years)

94/257 = died of prostate cancer/Number of deaths in group = 99/284

At a median follow-up of 7.8 years, 541 of 985 patients had died: 193 from prostate cancer & 183 from cardiovascular disease.

Overall survival hazard ratio was 1.25 favouring immediate treatment, seemingly due to fewer deaths from non-prostatic cancer causes (P = 0.06)

Time from randomisation to progression of hormone refractory disease did not differ significantly nor did prostate cancer-specific survival

Issues pertinent to extrapolating findings to routine clinical practice:

- Many urologists deferring androgen suppression therapy do not wait until patients develop symptoms from metastases or serious complications before commencing treatment
 - Unfortunate quirk of randomisation that the deferred group contained more patients (119/493) with Grade 3 tumours compared with the immediate group (110/492)
 - Treatment was not stratified to accommodate prostate cancer risk profiles
 - Median follow-up was only 7.8 years: as with MRC study, longer follow-up may result in different findings
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APPENDIX 10: TAX 327 & SWOG DOCETAXEL TRIALS ²⁰

The TAX 327 trial of Tannock *et al* ²²⁰ randomised 1006 patients to 3 weekly mitoxantrone plus prednisone (M/P), docetaxel weekly for 5 of 6 weeks or 3 weekly with prednisone (D/P). **The 3 weekly schedule of D/P showed a significantly improved overall survival compared with M/P, with the risk of death reduced by 24%** leading to a median survival prolongation of 2.5 months (18.9 against 16.5 months). In addition, there were **significant benefits in terms of decreased PSA levels, analgesic responses and patient-reported QoL assessment in the D/P group**. Toxicity was lowest in the M/P arm, while the highest in the weekly D/P group. This group did not show a survival benefit, so it was concluded that the three weekly schedule of D/P was optimal.

The SouthWest Oncology Group (SWOG) and accrued 674 eligible patients to either receive M/P or docetaxel and estramustine (D/E) three weekly ²²¹. Using the primary overall survival endpoint, **a significant benefit was found for the D/E arm, with the median survival increasing from 15.6 to 17.5 months** associated with a hazard ratio of 0.80. **PSA declines of >50% were seen in 50% of D/E men**, and 27% of those on M/P (p<0.001). **Pain relief was not significantly different between the arms and there was substantially more toxicity in those having D/E**, although the neutropenia rates were comparable

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