PASS IT ON!

For internal Hospital Authority use

實EVIDENCE証

Hospital Authority Head Office
Professional Services & Medical Development Division

Clinical Effectiveness Unit
Issue 15, 2001

Issues of concern in treatment of advanced prostate cancer

(This review does not include treatment of androgen refractory prostate cancers)

Summary

Is there any difference in effectiveness among the different androgen deprivation monotherapies?	1. Orchidectomy, diethylstilboestrol (DES)*, LHRH agonists and steroidal antiandrogen, given soon after diagnosis or deferred until symptom progression, have no significant difference in overall survival or disease progression-related outcomes. (Level Ia evidence) ** The VACURG trial reported excessive cardiovascular deaths in patients who received high dose DES (5.0 mg/d).* 2. Nonsteroidal antiandrogens showed a trend, short of statistical significant upon meta-analysis, of lower overall survival than orchidectomy, DES, or LHRH agonists. (Level Ia evidence) 3. There is scanty evidence on quality of life (QOL) and other outcome measures. 4. Side effects of orchidectomy, DES, LHRH agonists and antiandrogen differ. The evidence on differences in side effects among agents within each class is limited, and does not suggest that one is superior to the others.
Is combined androgen blockade more effective than monotherapy?	1. There is no significant improvement in overall survival upon addition of antiandrogen to orchidectomy or LHRH agonist, when trials using steroidal and nonsteroidal antiandrogens are included for analysis. If analysis is limited to trials using nonsteroidal antiandrogen, a modest but statistically significant improvement in 5-year survival is observed with combined androgen blockade. (Level Ia evidence, >80% of patients had metastases and remaining had locally advanced disease) 2. There is scanty evidence on QOL. 3. Pooled RCT data revealed more frequent adverse events and a higher treatment withdrawal rate in CAB than monotherapy.
Is there any difference in effectiveness between early and deferred androgen deprivation?	No RCT compared immediate vs deferred CAB. The following evidence was confined to monotherapies. 1. Androgen deprivation as initial therapy: For patients with previously untreated asymptomatic metastatic and locally advanced prostate cancer, evidence is inconclusive (both in quantity and quality)[ψ] whether early androgen deprivation would confer survival benefit over deferred treatment strategy. 1 RCT found striking reduction of serious complications in the early treatment arm. Considering deficiency in its study design, the main lesson learnt is that surveillance for disease progression must be more stringent to avoid complications when treatment is deferred. *[ψ] None of the trials had a uniform protocol for initiating deferred treatment, which therefore reflected prevailing local practices at the time of study. This introduced confounding variables causing disadvantage to the deferred treatment arm. Furthermore, the VACURG trials were conducted in the 1960s and represent a markedly older and sicker population than most patients would present nowadays, which makes their results not readily generalisable.*

	2. Androgen deprivation as adjuvant therapy: • For patients with advanced prostate cancer, some evidence (meta-analysis of 4 RCTs) suggests that early androgen deprivation, given as an adjuvant therapy to external beam radiation, can improve 5-year overall survival than if a deferred strategy is adopted. • For patients whose disease were clinically localized but histology revealed regional lymph node involvement, 1 RCT (of 98 participants) reported enhanced survival and reduced risk of recurrence when adjuvant androgen deprivation was given early than deferred. 3. Androgen deprivation as salvage therapy for relapse after prostatectomy or radiotherapy of initially localized disease: • There is no evidence on the effect of early vs deferred treatment. Although biochemical monitoring allows earlier detection of disease progression, there is currently neither evidence nor consensus on the optimal timing for initiating androgen deprivation in such conditions.
What is the role of intermittent androgen deprivation?	1. There is insufficient evidence on the effect of intermittent androgen deprivation, which should be considered investigational.
Unresolved issues due to insufficient / poor quality evidence	1. The relative effectiveness of different treatment options in terms of QOL. 2. The effectiveness of adjuvant therapy in locally advanced/ regional metastatic prostate cancers: • adding short-term androgen deprivation to radiotherapy • adding brachytherapy boost to external beam radiotherapy • adding radiotherapy or androgen deprivation to radical prostatectomy

	Metastatic Prostate Cancer	Locally advanced Prostate Cancer
Treatment objectives	a) To prevent/ delay disease progression b) To delay/ alleviate symptoms and morbidity c) To prolong survival d) To improve quality of life e) To minimize treatment side effects	a) To eradicate/ control primary tumor b) To prevent/ delay disease progression c) To delay/ alleviate symptoms and morbidity d) To prolong survival e) To improve quality of life f) To minimize treatment side effects
Treatment options	Androgen deprivation (unless or until tumor becomes refractory) a) Monotherapy • Orchidectomy (bilateral total or subscapular) • Oestrogen (obsolete), long acting luteinizing hormone-releasing hormone (LHRH) agonist, antiandrogen b) Combined (maximum) androgen blockade (CAB)	a) Radiotherapy ± adjuvant androgen deprivation b) Androgen deprivation c) Radical prostatectomy ± adjuvant radiotherapy or androgen deprivation d) Investigational • Radiotherapy ± neoadjuvant (short-term) androgen deprivation • External beam irradiation ± brachytherapy boost
Considerations in choosing treatment	a) Risk of spinal cord compression, ureteral obstruction (demanding quick response) b) Life expectancy (age, co-morbidities, etc) c) Symptoms d) Treatment side effects and patient preference	a) Tumour histology, Gleason score b) Degree of extracapsular extension (if resected specimen available for pathological examination) c) Life expectancy (age, co-morbidities) d) Treatment side effects and patient preference

Comparing androgen deprivation monotherapies

1. DES vs orchidectomy

3 RCTs (n=1,296) compared DES (1.0 and 5.0 mg/d) with orchidectomy and showed **no statistical significant difference in overall survival** (median survival and percentage of patients alive at 1, 2 and 5 years). The VACURG trial, conducted during 1960 – 1975, showed no difference in survival at 10 years after randomization.

[Source: Byer DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. NCI Monographs. 1988;7:165-70.

Aronson N, Seidenfeld J, Samson DJ, Albertson PC, Bayoumi AM, Bennett C, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostatic cancer [online]. Rockville, MD: Agency for Health Care Policy and Research. 1999 May. Evidence Report/Technology Assessment: No. 4. AHCPR Publication No. 99-E0012. Available from: URL: http://text.nlm.nih.gov/ftrs/dbaccess/prost.]

2. LHRH agonist

i) **LHRH agonist, as a class, showed no statistically significant difference in overall survival to orchidectomy or DES.** 10 RCTs (n=1908) compared an LHRH agonist with orchidectomy or DES. None of the 9 trials that reported survival outcomes found a statistically significant difference between treatments. Meta-analysis showed that 2-year overall survival with LHRH agonist (as a class) was similar to orchidectomy (hazard ratio 1.1262; 95%CI 0.915 to 1.386).

ii) **Different LHRH agonists yielded similar overall survival compared to orchidectomy.** Hazard ratio of leuprolide, goserelin and buserelin (compared to orchidectomy) was 1.0994 (95%CI 0.207 to 5.835), 1.1172 (95%CI 0.898 to 1.390) and 1.1315 (95%CI 0.533 to 2.404) respectively, by meta-analysis.

iii) **Evidence favoured no significant difference in progression-related outcomes compared to orchidectomy or DES.** 4 out of 5 studies reporting progression-related outcomes showed no difference. 1 study reported benefit in favour of orchidectomy or DES ($p<0.05$).

iv) **No significant difference in time to treatment failure compared to orchidectomy or DES.** 1 out of 5 studies almost achieved statistical significance in favour of goserelin over DES (24 % vs 35% survival at 2 years; $p = 0.06$).

3. Antiandrogen

i) **Nonsteroidal antiandrogens showed a trend (varying evidence and overall not significant) of lower overall survival than orchidectomy, DES, or LHRH agonists**. 8 RCTs (N=2717) compared a nonsteroidal antiandrogen to orchidectomy, DES, or an LHRH agonist. 3 of them showed significant difference in survival favouring control, with longer median survival and an 6-15% more patients surviving at 2 years. Meta-analysis of all studies showed hazard ratio for nonsteroidal antiandrogen to be 1.2158 (95%CI 0.988 to 1.496) compared to orchidectomy, 0.9835 (95%CI 0.764 to 1.267) compared to DES, and 1.1262 (95%CI 0.915 to 1.386) compared to LHRH agonists.

ii) **Evidence does not suggest difference between bicalutamide and flutamide.** Meta-analysis showed that the hazard ratio relative to orchidectomy was 1.2027 (95%CI 0.973 to 1.487) for bicalutamide and 1.9583 (95%CI 0.369 to 10.394) for flutamide.

iii) **Steroidal antiandrogen showed no statistically significant difference in overall survival to orchidectomy.** Meta-analysis showed that the hazard ratio relative to orchidectomy was 1.2005 (95%CI 0.592 to 2.433) for cyproterone, which was similar to that of the nonsteroidal antiandrogens.

iv) **No significant difference in progression-related outcomes compared to orchidectomy or DES.** Trials that compared an antiandrogen with DES or orchidectomy generally found no difference between the treatment arms or a modest benefit in favour of control. 2 identical trials comparing bicalutamide vs orchidectomy or goserelin showed conflicting results.

4. Treatment side effects

Treatment side effects have implications over effectiveness, QOL and patient preference. DES is rarely used nowadays, part of the reason being an excessive risk of cardiovascular death reported with 5.0 mg/d dose. Orchidectomy, LHRH agonists and antiandrogens differ in their side effects but precise and comprehensive comparison is not available in the current evidence. An attempt to compare treatment side effects was made in the AHCPR report by pooling data across different clinical trials. The validity of such an approach is limited by (i) unmatched patient population and other confounding variables between trials, (ii) inconsistency in the definition, assessment and reporting of side effects, and (iii) the sample size and duration of exposure in most clinical trials are insufficient to detect rare side effects. Therefore, the following information must be interpreted with caution.

i) Treatment withdrawal: more common with nonsteroidal antiandrogens (4-10%) than cyproterone (1-4%) or LHRH agonists (0-4%).

ii) Impotence: more common with orchidectomy (13%) or LHRH agonists (21%) than nonsteroidal antiandrogens (5%), but the available data are too inconsistent to quantify the differences.

iii) Hot flashes: more common with orchidectomy or LHRH agonists (about 50%) than nonsteroidal antiandrogens (about 11%).

iv) Gynecomastia: more common with nonsteroidal antiandrogens (about 38%) than orchidectomy or LHRH agonists (about 5%).

v) The evidence on differences in side effects among the agents within each class is limited, but does not suggest that one agent is superior to the others.

[Source: Aronson N, Seidenfeld J, Samson DJ, Albertson PC, Bayoumi AM, Bennett C, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostatic cancer [online]. Rockville, MD: Agency for Health Care Policy and Research. 1999 May. Evidence Report/Technology Assessment: No. 4. AHCPR Publication No. 99-E0012. Available from: URL: http://text.nlm.nih.gov/ftrs/dbaccess/prost.

Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen P, Bennett CL, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med. 2000 Apr 4;132(7):566-77.

Note. Identical review. Most patients recruited to the RCTs relating to comparison of monotherapies belonged to D2 or M1.*]*

Comparing Combined Androgen Blockade (CAB) and Androgen Deprivation Monotherapy (AD)
3 meta-analyses (performed on largely similar primary trials)

1. Systematic review by the Prostate Cancer Trialists' Collaborative Group

Trials & participants	Regimen	Main findings	Interpretation
27 RCTs, recruited 8275 men with advanced prostate cancer (88% metastatic & 12% locally advanced). Most trials were FU for about 5 years (0-4), 5932 men have died. All trials provided update information. Review reanalyzed individual data	CAB: AD + antiandrogen (for ≥1 year or until progression) AD: 'orchidectomy or LHRH agonist' ± placebo.	<u>All trials:</u> i) Death rate ratios at year 0, 1-2, 3-4 and 5 are not significant in favor of either treatment arm ii) 5-year survival is 25.4% (CAB) vs 23.6% (AD); SE 1.3; logrank 2p=0.11 (statistical not significant) iii) Projected 10-year survival is 6.2% (CAB) vs 5.5% (AD) Breakdown wrt antiandrogen: Survival generally favored CAB with nonsteroidal antiandrogen (flutamide or nilutamide) and generally less favorable for CAB with cyproterone. i) Flutamide or nilutamide (20 trials, 6500 men). 5-year survival is 27.6% (CAB) vs 24.7% (AP); SE 1.3; logrank 2p=0.005 ii) Cyproterone (7 trials, 1784 men). 5-year survival is 15.4% (CAB) vs 18.1% (AP); SE 2.4; logrank 2p=0.04 Subgroup analysis reveals an excess of non-prostate cancer deaths in trials of cyproterone and not in those of nilutamide or flutamide. This should account for some of the apparent adverse effect of cyproterone. Subtracting non-prostate cancer deaths from analysis makes outcome more favourable for CAB but it still fails to achieve the conventional level of statistical significance. There was no significant heterogeneity in survival wrt age (65 vs 65-74 vs ≥75) or disease stage (no metastases vs definite metastases).	Analysis of all trials does not reach statistical significance. Outcome apparently varied with the antiandrogen used. Even excluding trials involving cyproterone, the magnitude of difference for 5-year survival is small: ARR 2.9%, with 95%CI 0.4% to 5.4%. **The review did not address other medical outcomes, quality of life, or treatment costs, and the collaborative group makes no comment on whether, if real, a difference of a few percent in a five-year survival should be considered clinically significant.**

2. Systematic review by the Cochrane Review Group

<table>
<tr><th>Trials & participants</th><th>Regimen</th><th>Main findings</th><th>Interpretation</th></tr>
<tr>
<td>20 RCTs, recruited 6320 men with advanced prostate cancer.</td>
<td>Nonsteroidal antiandrogen (NSAA) + castration vs castration alone</td>
<td>
Pooled odds ratio (OR) of ‘overall survival’ increased progressively over time favouring CAB at 5 years (reached conventional level of statistical significance). Concerning the magnitude of treatment effect, pooled risk difference (RD) increased (and NNT correspondingly decreased) over time:
<table>
<tr><th></th><th>at 1 yr (95%CI)</th><th>at 2 yr (95%CI)</th><th>at 5 yr (95%CI)</th></tr>
<tr><td>Odds Ratio (OR)</td><td>1.03 (0.85 to1.25)</td><td>1.16 (1.00 to 1.33)</td><td>1.29 (1.11 to 1.50)</td></tr>
<tr><td>Risk Difference (RD)</td><td>0.003 (-0.022 to0.028)</td><td>0.032 (0.000 to 0.064)</td><td>0.048 (0.02 to 0.077)</td></tr>
<tr><td>Number need to Treat (NNT)</td><td>333.3 (na to 35.7)</td><td>31.3 (na to 15.6)</td><td>20.8 (50 to 12.9)</td></tr>
</table>
Subgroup analysis showed same trend of progressive increase in OR of ‘overall survival’ over time. It is not possible to determine if important difference exists between types of monotherapy or NSAA:
<table>
<tr><th></th><th>OR at 1 yr (95%CI)</th><th>OR at 2 yr (95%CI)</th><th>OR at 5 yr (95%CI)</th></tr>
<tr><td>Limit to trials with >90% M1 disease</td><td>1.10 (0.86 to 1.41)</td><td>1.10 (0.92 to 1.32)</td><td>1.25 (1.05 to 1.48)</td></tr>
<tr><td>Limit to high quality trials</td><td>1.02 (0.67 to 1.55)</td><td>1.21 (0.93 to 1.32)</td><td>1.34 (0.96 to 1.87)</td></tr>
<tr><td>Flutamide + orchidectomy vs orchidectomy</td><td>0.68 (0.25 to 1.87)</td><td>0.85 (0.52 to 1.41)</td><td>1.22 (0.97 to 1.53)</td></tr>
<tr><td>Flutamide+ LHRH agonist vs monotherapy</td><td>1.07 (0.84 to 1.35)</td><td>1.21 (0.97 to1.50)</td><td>1.30 (1.05 to 1.60)</td></tr>
<tr><td>Nilutamide +orchidectomy vs orchidectomy</td><td>1.24 (0.88 to1.74)</td><td>1.2 8 (1.02 to 1.62)</td><td>1.68 (1.00 to 2.83)</td></tr>
</table>
Pooled OR of ‘progression-free survival’ was significant only at 1 year followed-up:
<table>
<tr><th></th><th>OR at 1 yr (95%CI)</th><th>OR at 2 yr (95%CI)</th><th>OR at 5 yr (95%CI)</th></tr>
<tr><td>All trials</td><td>1.38 (1.15 to1.67)</td><td>1.19 (0.97 to 1.46)</td><td>1.14 (0.77 to 1.68)</td></tr>
</table>
Pooled OR of ‘cancer-specific survival’ increased over time and was significant at 5 years:
</td>
<td>
CAB (with nonsteroidal antiandrogen) produces a modest improvement in overall and cancer-specific survival at 5 years but is associated with increased adverse events and possibly a reduction in QOL.

Only a small number of trials provided 5-year FU data for overall and cancer-specific survival (raising the possibility of publication bias).
</td>
</tr>
</table>

		OR at 1 yr (95%CI)	OR at 2 yr (95%CI)	OR at 5 yr (95%CI)
		All trials	1.20 (0.92 to 1.57)	1.22 (0.86 to1.73)	**1.58 (1.05 to 2.37)**
		Adverse events (pooled) were more frequent in CAB than AD treatment: diarrhoea (9.7% vs 1.8%); GI pain (7.4% vs 1.6%); non-specific ophthalmologic events (29% vs 5.4%). Withdrew rate was 10% vs 4% for CAB and AD. There is scanty evidence on quality of life (QOL). 1 RCT (n=739, stage M1) showed that patients who received 'orchidectomy + placebo' had better self QOL assessment over diarrhoea and emotional functioning in the first 6 months (study period) than those received 'orchidectomy + flutamide'.			

[*Source: Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer. In: The Cochrane Library [online], Issue 3, 2001. Oxford: Update Software. (Last substantive amendment: 14 Jan, 1999)*
Note: meta-analyses utilized a random effect model.]

3. Systematic review by the Blue Cross and Blue Shield Association for the Agency for Health Care Policy and Research

Trials & participants	Main findings
28 RCTs ◆ 20 (n = 6085) compared CAB (used NSAA) with monotherapy. (most studies compared orchidectomy, leuprolide, or goserelin with the same monotherapy + 'flutamide or nilutamide'. ◆ 7 (n = 1902) compared CAB (used steroidal antiandrogen) with monotherapy. ◆ 1 (n = 813) compared 4 CAB regimens. Of these, 20 trials recruited only metastatic diseases. 12 trials accepted only stage D2/M1, 8 trials also accepted metastases to the regional LN (range 3-30%)	21 RCTs: 18 (n=5,485) showed no significant difference in overall survival and 3 (n=1,386) reported a statistically significant difference in overall survival favoring CAB (3.7 to 7 months longer median survival and 3-9% higher 5-year survival rate). Meta-analysis found **statistically significant better overall survival for CAB at 5 years (hazard ratio 0.871; 95%CI 0.805 to 0.942) but not at 2 years (hazard ratio 0.970; 95%CI 0.866 to 1.087)**. Meta-analysis of 5-year survival was performed on data from 66% of patients since only 10 trials reporting 2-year survival also reported 5-year survival. Sensitivity analyses suggest that if complete 5-year data were available for all trials, the magnitude of benefit would not be of greater clinical significance: estimated pooled hazard ratio for 5-year survival would be 0.9146 (95%CI 0.8461 to 0.9887). *6 RCTs: **CAB and monotherapy showed no statistically significant difference in survival for patients with good prognosis**. 4 trials, including the SWOG Intergroup trial (INT 0105) which was prospectively designed and with adequate power to compare outcomes by prognostic subgroups, found no statistically significant differences in outcome between CAB and monotherapy. 2 trials reported better survival in the CAB arm for patients with good prognosis but did not specify whether the differences were statistically significant.* 4 RCTs: **different nonsteroidal antiandrogens in CAB did not produce different survival outcome**. Of the 3 trials that reported a statistically significant difference in survival favoring CAB, 2 used flutamide and 1 used nilutamide. The hazard ratio is 0.878 (95%CI 0.564 to 1.368) in trials using nilutamide and 0.945 (95%CI 0.779 to 1.147) in trials using flutamide. In the only trial that directly compared different CAB regimens, there was no statistically significant difference in survival between treatment regimens with flutamide or bicalutamide (hazard ratio 0.87; 95%CI 0.72 to 1.05). The evidence comparing adverse effects is limited, but favours monotherapy over combined androgen blockade. Evidence comparing quality of life was available from only one study and also favored monotherapy. (Same findings as in the Cochrane review)

[Source: Aronson N, Seidenfeld J, Samson DJ, Albertson PC, Bayoumi AM, Bennett C, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostatic cancer [online]. Rockville, MD: Agency for Health Care Policy and Research. 1999 May. Evidence Report/Technology Assessment: No. 4. AHCPR Publication No. 99-E0012. Available from: URL: http://text.nlm.nih.gov/ftrs/dbaccess/prost.

Immediate vs Deferred Androgen Deprivation

As response to androgen deprivation is temporary and disease becomes rapidly fatal following relapse, there are ongoing debates about the optimal timing of hormone therapy.

No RCT compared immediate vs deferred CAB. Evidence was confined to monotherapies.

1. Newly diagnosed locally advanced and asymptomatic metastatic disease:

i) VACURG Study 1: Immediate androgen deprivation (orchidectomy, 5.0 mg DES/day) delayed disease progression from stage III (locally advanced) to IV (metastatic) compared to the 'placebo' (deferred treatment). However, study showed no survival advantage in either stage III or stage IV patients, partly because of excessive cardiovascular deaths in the DES-treated arms.

ii) VACURG Study 2: Immediate androgen deprivation (1.0 mg DES/day) improved overall survival in stage III and IV patients (pooled) compared to 'placebo' treatment. Difference was modest for the first 3 years but approximately 10-12% more patients survived at 5, 6 and 7 years.

iii) MRC trial (interim result): immediate treatment was associated with improved overall and cancer-specific survivals reaching statistical significant (largely contributed by patients with stage M0 at randomization). There were also striking reductions serious complications caused by prostate cancer.

Outcomes$^{\Omega}$	Immediate AD (n=469)	Deferred AD (n=465)	p, two-tailed
Death (all causes)*	328 (69.9%)	361 (77.6%)	= 0.02
Death (cancer-specific)*	203 (43.3%)	257 (55.3%)	= 0.001
Cord compression	9 (1.9%)	23 (4.9%)	< 0.025
Ureteric obstruction	33 (7.0%)	55 (11.8%)	< 0.025
Required TURP	65 (13.8%)	141 (30.3%)	< 0.001
Extra-skeletal metastases	37 (7.9%)	55 (11.8%)	< 0.05
Pathological fracture	11 (2.3%)	21 (4.5%)	Not significant

$^{\Omega}$ Length of follow-up was not provided. (Note that patients were recruited during 1985 to 1993, and the report was accepted for publication in 1996.)
* Sub-group analysis showed that difference was significant for M0 but not for Mx or M1 patients. (Mx: no evidence of metastases but status not confirmed by bone scan)

Meta-analysis of 3 RCTs: hazard ratio of overall survival for immediate vs deferred treatment is 0.914 (95%CI 0.815 to 1.026), close to but just fall short of the conventional level of statistical significance. Evidence is insufficient to be conclusive.

[Source: Byer DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. NCI Monographs. 1988;7:165-70.

The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate vs deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. Br J Urol. 1997 Feb;79(2):235-46.

Aronson N, Seidenfeld J, Samson DJ, Albertson PC, Bayoumi AM, Bennett C, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostatic cancer [online]. Rockville, MD: Agency for Health Care Policy and Research. 1999 May. Evidence Report/Technology Assessment: No. 4. AHCPR Publication No. 99-E0012. Available from: URL: http://text.nlm.nih.gov/ftrs/dbaccess/prost.]

[***Editorial note***: None of the 3 trials had a uniform protocol for initiating deferred treatment, which therefore reflected prevailing local practices at the time of study. This

introduced confounding variables causing disadvantage to the deferred treatment arm. Furthermore, the VACURG trials were conducted in the 1960s and represent a markedly older and sicker population than most patients would present nowadays, which makes their results not readily generalizable.]

2. Disease progression after definitive treatment for initially localized prostate cancer:
No published data on optimal timing in initiating androgen deprivation.

3. As adjuvant therapy to definitive treatment for patients with locally advanced or asymptomatic metastatic prostate cancer:

i) 4 RCTs (n = 1565) compared early vs deferred androgen deprivation as adjuvant to external beam radiation. Two of them (n = 506) reported statistically significant better 5-year overall survival (79% vs 62%, p = 0.001 and 83% vs 69%, p = 0.02) in favor of early androgen deprivation. The other two (n = 1,059) found no statistically significant difference, but subgroup analysis in one of the studies showed a statistically significant difference in 5-year overall survival (66% vs 55%, p=0.03) in favor of early androgen deprivation in patients with Gleason scores of 8-10).

Meta-analysis suggested improved 5-year overall survival with early androgen deprivation: hazard ratio 0.631 (95%CI 0.479 to 0.831); 5-year survival rate 76.5% vs 68.2% (ARR 8.3%, NNT = 12).

[Source: Aronson N, Seidenfeld J, Samson DJ, Albertson PC, Bayoumi AM, Bennett C, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostatic cancer [online]. Rockville, MD: Agency for Health Care Policy and Research. 1999 May. Evidence Report/Technology Assessment: No. 4. AHCPR Publication No. 99-E0012. Available from: URL: http://text.nlm.nih.gov/ftrs/dbaccess/prost.]

[***Editorial note***: None of these trials included a treatment arm of androgen deprivation alone. There is no evidence to determine whether radiotherapy plus androgen deprivation increases survival over androgen deprivation.]

ii) 1 RCT (n = 98, clinically localized but histology revealed regional node metastases) reported that starting androgen deprivation shortly (within 12 weeks) after radical prostatectomy and pelvic lymphadenectomy improved survival and reduced risk of recurrence compared to deferred treatment (upon signs of progression other than PSA change).

Outcomes after a median follow-up of 7.1 years by intention-to-treat analysis:

Outcomes		Deferred AD (n=51)	Early AD (n=47)	Hazard ratio (95%CI)	p
Dead (all causes)		18	7	3.0 (1.2 – 7.3)	0.02
Dead (cancer-specific)		16	3	6.2 (1.8 – 21.5)	<0.01
Recurrence (including PSA change)		42	7	12.2 (5.1 – 29.1)	<0.001
Alive with no evidence of disease		23	36		
Adverse effects	Mild to moderate	115	28		
	Severe	7	3		
	Life-threatening	2	0		

[Source: Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999 Dec 9;341(24):1781-8.]

[***Editorial note***: The strategy of deferring treatment upon signs of disease progression should entail a higher recurrence rate. It is more relevant to compare survival, serious complications and quality of life between the two treatment strategies.]

Androgen deprivation vs Radiotherapy vs Combined Radiotherapy & Androgen Deprivation

Scanty evidence. 1 RCT (n = 277) compared androgen deprivation (orchidectomy) vs radiotherapy vs radiotherapy + orchidectomy in locally advanced prostate cancer (T2-T4NXM0). It found no significant differences between the 3 treatment arms in terms of overall survival or need for further treatment for local disease progression.

[Source: Fellow GJ, Clark PB, Beynon LL, Boreham J, Keen C, Parkinson MC, et al. Treatment of advanced localised prostatic cancer by orchiectomy, radiotherapy, or combined treatment: a Medical Research Council study. Br J Urol. 1992 Sep;70(3):304-9.]

This publication is the collaborative efforts between the Clinical Effectiveness Unit, HAHO and the following experts: Drs Richard Lo Kwong Yin, Man Chi Wai, Tam Po Chor, Wong Wai Sang, Bill Wong Tak Hing and Yiu Tim Fuk.