

# Androgen deprivation therapy for prostate cancer – the potential of parenteral estrogen

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## KEY WORDS

prostate cancer ▶ androgen deprivation therapy  
▶ andropause ▶ estrogen ▶ drug administration routes

## ABSTRACT

The treatment of choice for carcinoma of the prostate for over a generation was oral estrogen but this was abandoned due to an excess of cardiovascular and thromboembolic toxicity. We now recognize that most of this toxicity relates to first pass portal circulation where hepatic metabolism of hormones, lipids and coagulation proteins is up regulated. It has been shown that most of such toxicity can be avoided by parenteral (intramuscular or transdermal) estrogen administration; this avoids hepatic enzyme induction. A modest short term increase in cardiovascular morbidity (but not mortality) is compensated for by a long term cardioprotective benefit, which accrues progressively as vascular remodeling develops with time. A major advantage of estrogen therapy is protection against the effects of the andropause (cf female menopause), which with conventional androgen suppression causes significant morbidity including osteoporotic fracture, hot flushes, lethargy and cognitive dysfunction. Parenteral estrogen therapy is also much cheaper than contemporary endocrine therapy, with substantial economic benefits for health providers.

## INTRODUCTION – A HISTORICAL PROSPECTIVE

In 1941, the first description of clinical response to estrogen therapy in advanced carcinoma of the prostate (CaP) was published by Charles Huggins [1]. Two subsequent large, but retrospective analyses concluded that estrogens improved survival for all stages (early and late) of disease [2, 3]. Estrogens (and orchidectomy) became the management of choice for over three decades. Through recognition of hormonal influences on CaP and the potential to manipulate its natural history by androgen suppression, Huggins received the Nobel Prize, the only urologist ever to receive such an honor.

The Veterans Administration Cooperative Urological Research Group (VACURG) performed the first controlled studies during the 1970s. These studies demonstrated a discrepancy between disease-specific survival and overall survival [4-6]. Oral estrogen achieved disease responses in up to 80% of patients and delayed disease progression (there is little evidence that any type of hormone manipulation improves overall survival). However, there was also a significantly increased risk of cardiovascular toxicity in up to 35%, and especially thromboembolism in 15%. VACURG concluded that

estrogen therapy should be reserved for men with advanced and symptomatic disease [6]. Research into and use of estrogen therapy rapidly declined as the development of luteinizing hormone releasing hormone (LHRH) agonists and non-steroidal anti-androgens (NSAA) followed.

Contemporary androgen suppression therapy is now based on the use of LHRH agonist, NSAA or orchidectomy. Whilst associated with a lower incidence of cardiovascular toxicity compared to oral estrogen, there remains significant morbidity. Hypogonadism results in accelerated osteoporosis and a significant increase in the risk of osteoporotic fracture [7, 8]. The occurrence of an andropausal state (also called castration syndrome) is characterized by hot flushes, loss of libido, reduced energy, sarcopenia and cognitive dysfunction [9, 10]. With emerging data suggesting that starting androgen suppression earlier in the natural history of CaP may improve outcome [11-13], it is important to recognize that long term androgen deprivation may itself be the cause of complications that were not intended. By contrast, estrogen as hormone replacement therapy (HRT) is the established therapy for menopause in women [14]. Therefore, if estrogen could be delivered without cardiovascular toxicity but with the advantages of the estrogenic environment, this could offer an attractive proposition in CaP.

## Mechanisms of estrogen toxicity – dosage, route of administration, vascular flow, and time. Toxicity (and clinical response) is related to dose

Three mg diethylstilboestrol (DES) was established as 'standard' dose and equivalent to castrate levels of testosterone [15] despite the VACURG studies showing a lower 1 mg dose had equivalent oncological effect and also reduced cardiovascular toxicity [5]. Non-cancer related mortality in the 3 and 5 mg DES VACURG treatment arms studies was 29.6% compared to 21.6% for the non-estrogen treatments (relative risk of estrogen-related cardiovascular mortality 1.45). The difference was accounted for by an excess of cardiovascular mortality (17.0% versus 11.7%), manifesting within the first months after treatment began. The risk of serious cardiovascular morbidity with 3 mg DES is now accepted to average between 30 and 35% [16-19]. One mg of DES was associated with significantly lower cardiovascular toxicity; cardiovascular morbidity was 21%, similar to that observed in the non-estrogen arms [5].

In 1995, the European Organization into Research and Treatment of Cancer (EORTC) compared orchidectomy versus orchidectomy plus cyproterone acetate (maximum androgen blockade (MAB)) versus low dose 1 mg DES in patients with metastatic disease [20]. This was the first study since VACURG to reassess the efficacy and toxicity of low dose estrogen. There was no difference in time to progression or overall survival between treatment arms. Cardiovascular toxicity and mortality (14.8%) of 1 mg DES approached twice that of orchidectomy alone (8.3%). The difference was most apparent in men with a past history of cardiovascular disease. A smaller, single-institution study treated men with an initial dose of 1 mg DES daily, which was subsequently titrated to the

**Table 1.** Studies using parenteral estrogens for the treatment of men with advanced prostate cancer.

Study	Study Type	Patient Number	Median follow up (months)	Cardiovascular Risk/Complications (%)
<b>Finnprostate Studies</b>				
PEP versus orchidectomy (Haapiainen 1990) [68]	Comparative	200	24	Mortality 1.6% PEP versus 1.3% orchidectomy (morbidity not reported)
PEP versus orchidectomy (Aro 1991) [44]	Epidemiological	477	72	Relative cardiovascular risk 0.17 PEP versus 0.78 orchidectomy
PEP versus LHRH agonist (Aro 1988 / 1989 / 1993) [69]	Comparative	147	36	Morbidity 7.1% PEP versus 7.8% LHRH agonist Mortality 5.7% PEP versus 5.2% LHRH agonist
PEP versus LHRH agonist (Lukkarinen 1994) [70]	Comparative	236	23	Morbidity 19.6% PEP versus 9.3% LHRH agonists Mortality 6.5% PEP versus 6.2% LHRH agonist
PEP versus orchidectomy (Mikkola 1998 / 2005 / 2007) [36,43,71]	Randomized	444	24	Overall morbidity 6% PEP versus 1.4% orchidectomy, first year Overall morbidity 6% PEP versus 4% orchidectomy, second year (not significant) Overall morbidity 10.8% PEP versus 12.2% orchidectomy, ten year (not significant) T3-4 MO year 1-3 PEP (4.8%, 6.3%, 6.7%) versus orchidectomy (0.8%, 2.7%, 1.9%) T1-4 M1 year 1-3 PEP (8.8%, 4.7%, 0%) versus orchidectomy (2.0%, 6.3%, 2.9%)
<b>SPCG Studies</b>				
PEP (Henriksson 1988) [23]	Pilot	38	14.1	0%
PEP (Stege 1988) [24]	Pilot	27	6	0%
PEP (Stege 1989) [25]	Pilot	17	12	0%
Oral, PEP and Orchidectomy (Carlstrom 1989) [27]	Pilot	48	12	0%
PEP versus orchidectomy (Henriksson 1999) [45]	Randomized	33	24	6% PEP versus 24% orchidectomy (statistical analysis not provided)
PEP versus MAB (Hedlund 2000 / 2002 / 2008) [35,46,72]	Randomized	917	139	Overall mortality 60.9% PEP versus 61.3% MAB (not significant) Cardiovascular mortality 5.1% PEP versus 5.1% MAB (not significant) Cardiovascular morbidity 17.6% PEP versus 13.0% MAB
<b>Other Studies</b>				
PEP versus orchidectomy (Bishop 1989) [21]	Comparative	117	Not recorded	Morbidity PEP 13.1% versus 7.1% orchidectomy
Transdermal estradiol (Ockrim 2003) [26]	Pilot	20	12	Morbidity 5%

clinical, hormonal and prostate specific antigen (PSA) responses [21]. Although only 27% achieved castrate levels of testosterone with 1 mg DES, there was a sustained PSA response in 66%. In the 33% with PSA failure, doubling the DES dose led to a PSA response. Cardiovascular toxicity was noted in 7.5%, but only one life-threatening (thromboembolic) event occurred. Bishop [21] suggested that low dose estrogen titrated to response achieved acceptable toxicity levels for this group of men. Nevertheless, cardiovascular risk even at lower oral estrogen doses does not compare well to the of 3 to 6% cardiovascular mortality and 8 to 20% cardiovascular morbidity expected during treatment with orchidectomy or LHRH agonists [22]. Dose modulation for oral estrogen therapy was never pursued.

There is also a relationship between dose response and cardiovascular toxicity for parenteral estrogen therapy, but this is less well defined. A series of pilot studies in Scandinavia com-

pared 2 doses (160 mg / 240 mg) and different depot scheduling (induction and maintenance regimes) of polyestradiol phosphate (PEP) as first line hormone therapy to achieve rapid castrate levels of testosterone [23-25]. Numbers were small but the dose schedule established for their later large randomized controlled trials achieved castrate levels of testosterone in all patients and are presumably bioequivalent to 3 mg of oral DES. There was no cardiovascular toxicity in these pilot studies. The sole study of transdermal estradiol [26] also titrated dose to castrate testosterone levels. The serum estradiol levels achieved (Fig. 1) are also assumed to be equivalent to 3 mg DES. Bioequivalency between oral and parenteral estrogen administration remains incompletely resolved, but as the parenteral doses of estrogen in use have equivalent oncological effect to other hormone therapies, they can be considered valid clinical comparators when evaluating relative toxicities.

### Toxicity is related to route of administration

The adverse cardiovascular toxicity of oral estrogen therapy is essentially related to the route of administration. First pass hepatic exposure to high doses of estrogen via the portal circulation up-regulates metabolism of hormones, lipids and coagulation proteins, all contributing to the biochemical changes believed responsible for short and long term cardiovascular events [26-30]. Parenteral routes of administration (intravenous, intramuscular and transdermal) significantly reduce this exposure and the metabolic consequences. This can be shown objectively through the physiological ratios of sex hormones and their binding globulins. Oral estrogen results in multifold increases in the ratio of estradiol and its metabolites (particularly estrone), but this ratio remains unaffected by equivalent doses of parenteral estrogen [26, 27]. Similarly, physiological ratios of high density lipoproteins (HDL) and low DL (and other lipids) are reversed with oral estrogens, but cardioprotective ratios are preserved with parenteral estrogen administration [31].

Venous and arterial thromboembolism are the most apparent adverse effect of oral estrogens (transient ischemic attacks, cerebrovascular accidents and myocardial infarction) with marked increases in activated coagulation proteins (including factors VII, VIII, IX, X and fibrinogen), decreases in inhibitors of coagulation (anti-thrombin III, protein S and tissue factor pathway inhibitor) and increased levels of fibrinolytic factors (plasminogen, tissue plasminogen activator, and D-dimer) [29]. These changes do not occur with parenteral estrogens. Parenteral estrogen administration has been shown to reduce levels of thrombophilic activation (particularly prothrombin fragments F1 and F2, fibrinogen and D-dimer, Fig. 2) often associated with advanced prostate cancer [32]. Such thrombophilic data are supported by clinical studies (discussed below) including those of male to female gender reassignment patients, in which a twenty-fold increase in the incidence of thromboembolism was eliminated by a change from oral to transdermal estradiol [33].

### Toxicity related to changes in vascular flow over time

The other major determinant of estrogen toxicity relates to vascular changes in the arterial circulation over time. Arterial dilatation and an associated reduction in arterial compliance (stiff arteries) occur, which results in an increase in cardiac demands and capillary filtration. This results in increased peripheral and pulmonary edema and cardiac decompensation [34, 35]. This effect is time dependent and mostly manifests in the first few months (over 75% within the first 6 months) of estrogen initiation [17, 30, 36]. With time arterial compliance improves (Fig. 3), possibly due to estrogen driven vascular remodeling and improved cardiovascular dynamics [37, 38].

Epidemiological studies have repeatedly suggested estrogen therapy is cardioprotective. An overall risk reduction of 30-50% is reported [20]. It had been assumed that this vascular benefit was immediate, but the first prospective data from The Heart and Estrogen/progestin Replacement Study (HERS) [39] unexpectedly demonstrated an increase in cardiovascular events in the first year. A favorable cardiovascular effect was not established until 2 years after treatment began and the cardioprotective benefit increased consistently for the 3 years thereafter. A time trend was also shown in the Nurses' Health Study [40]. This showed women with baseline coronary artery disease also had a temporary increase in cardiovascular risk in the first year (relative risk 1.25), but a subsequent decrease in cardiovascular toxicity. Long-term users had a significant reduction in cardiac events up to 20 years (relative risk 0.65). Thus the effect of HRT appears time-dependent.

The dual mode of action that estrogen has on the vasculature may explain the different time effects. Immediate changes

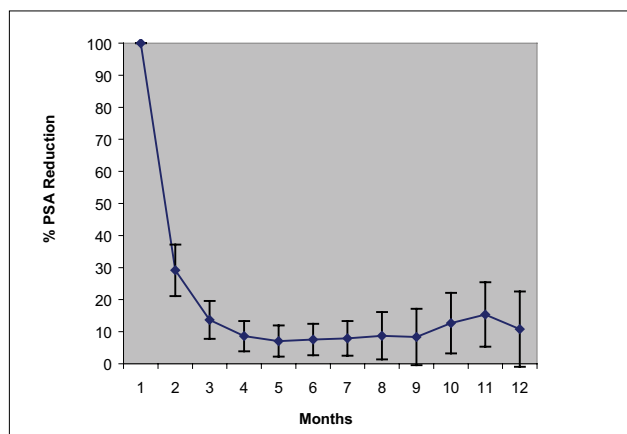
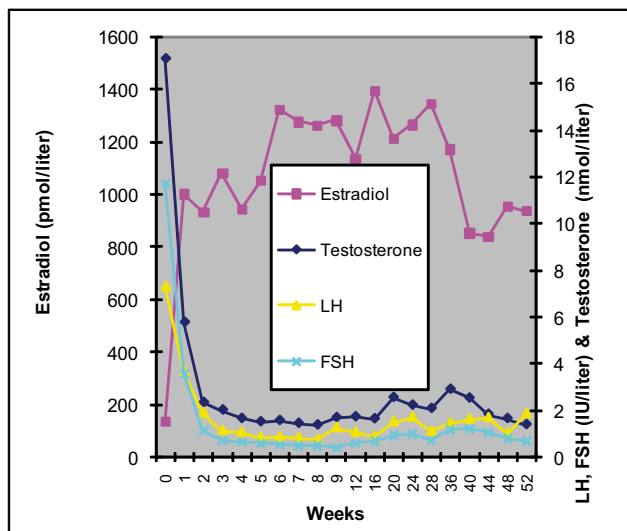


Fig. 1. Pituitary-testicular response to transdermal estradiol therapy and the PSA response (mean and standard error mean) over 12 months.

in vascular tone are mediated by the initiation of cellular events (endothelium-dependent vasodilatation). Long-term modulation of vascular compliance is a consequence of vascular remodeling. Cardiovascular benefit only accrues once vascular adaptation is sufficient to reduce overall cardiac workload [37, 38].

### Toxicity in clinical studies of parenteral estrogen

To date, there are only 13 studies on the use of parenteral estrogens in CaP (Table 1). The quality of the limited data available and especially variability of inclusion criteria, dose variability and outcome assessment have been reported elsewhere [41]. These studies and historical comparisons of oral estrogen and LHRH agonists however do suggest that cancer-specific efficacy is equivalent. Most toxicity data came from the two Scandinavian groups using intramuscular PEP. The Finnprostate studies compared PEP to orchidectomy and reported increased cardiovascular morbidity in the first 2 years of therapy (11% PEP versus 5% orchidectomy), a disparity that was only statistically significant within the first year [36]. By following 477 patients longitudinally for up to 10 years it appeared that this trend was subsequently reversed such that a relative cardiovascular risk was calculated at 1.51 with oral estrogens, 0.78 with orchidectomy, but only 0.17 using PEP [42]. The Finnprostate findings are supported by those of the Scandinavian Prostate Cancer Group (SPCG – 1 to 5 pilot studies), which together contain over 1000 patients (Table 1). SPCG-5 offers the only high quality (level 1 evidence) randomized study of parenter-

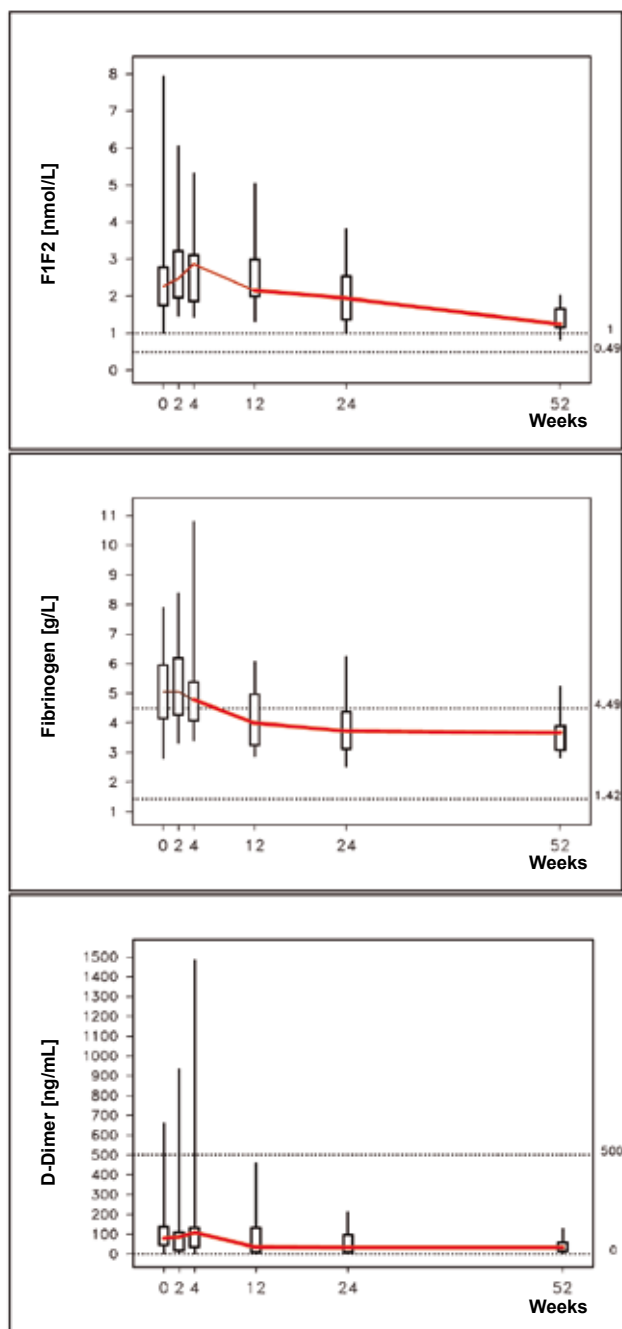


Fig. 2. Improved levels of prothrombin fragments F1+F2, fibrinogen, and D-dimer during transdermal estradiol therapy. The column whiskers represent min and max values, boxes first and third quartiles, red lines are connecting the medians and hatched lines are the normal ranges.

al estrogens and LHRH agonists published to date. This compared 917 men treated by PEP or MAB [30]. Cardiovascular morbidity in the PEP arm was substantially reduced compared to that expected from the equivalent dose of oral estrogen (expected oral estrogen toxicity up to 35% versus 12.5% PEP versus 7.9% MAB) even though the PEP arm had a higher prevalence of cardiovascular disease prior to study. Overall (60.9% PEP versus 61.3% MAB) and cardiovascular mortality (5.1% PEP versus 5.1% MAB) after median 139 months was equivalent. A modest increase in cardiovascular morbidity in PEP patients (17.6% PEP versus 13.0% MAB) was traded for reduced major skeletal morbidity (0% PEP versus 5.0% MAB) [30, 43, 72].

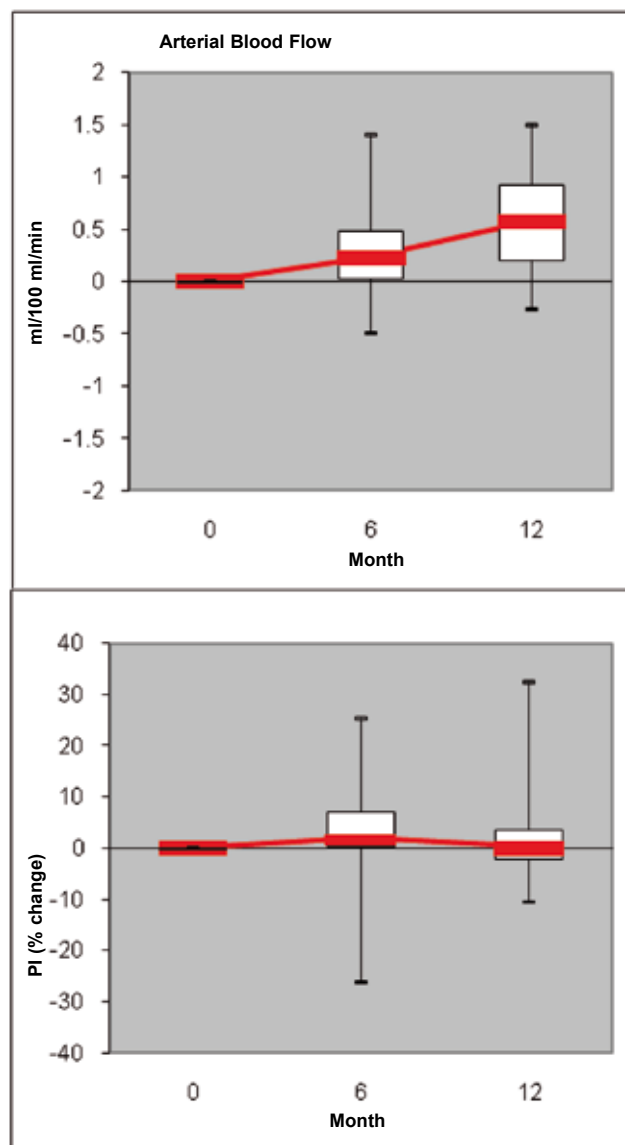


Fig. 3. Arterial blood and capillary filtration increase during transdermal estradiol therapy, a possible explanation for increased risk of edema and cardiac decompensation. Over time the arterial compliance (an inverse of the pulsatility index, shown here) initially reduces, but improves over the second 6 months of therapy. This explains the improved vascular dynamics and cardioprotective benefits that accrue subsequently.

#### Advantages of parenteral estrogen therapy and disadvantages of current androgen suppression therapies – introduction

After the VACURG studies [4–6], endocrine therapy was limited to those with advanced and mostly symptomatic disease as the anticipated length of therapy was short, palliative treatment effect most marked and the benefits of therapy more easily outweighed any long-term side effects. Recently the management of CaP has become more complex with renewed interest in the timing and nature of hormonal interventions. This is related to several factors including the stage shift at diagnosis caused by PSA screening, the larger number of endocrine treatment options available to clinicians and expectations of effective therapy by patients. Present best evidence suggests early hormonal therapy may offer survival benefit to CaP patients with nodal metastases or biochemical failure after radical prostatectomy (and as neoadjuvant/adjuvant to radical radiotherapy) [11, 13]. Recognition that early hormonal therapy for these men, and also those with early asymptomatic (high grade) metastatic disease, may delay progression and reduce

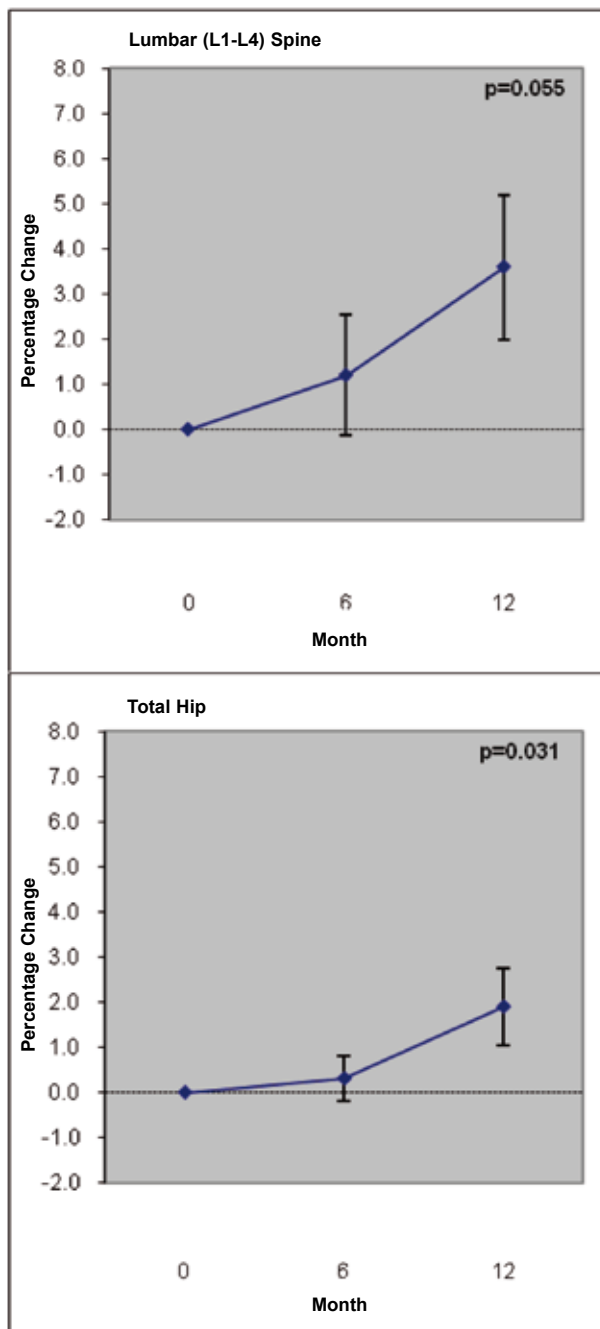


Fig. 4. Changes in bone mineral density in men treated with transdermal estradiol patches over one year. Bars represent means and standard error of mean.

both symptoms and complication rates is equally important [12]. Many urologists now treat men with androgen suppression much earlier in the natural history of the disease. Therefore many men are exposed to hormonal therapy for significantly longer times [44] and the disparity between palliative benefit and accumulation of toxicity becomes less distinct. Where long term endocrine therapy is anticipated, the impact on overall quality of life (QOL), normal function and treatment-related side effects have become equally as important as disease outcome. Parenteral estrogen therapy could offer significant QOL advantages over contemporary hormone therapies.

**Parenteral estrogen therapy and osteoporosis**

Urologists and the wider medical community recognize bone loss from protracted androgen suppression to be of increasing

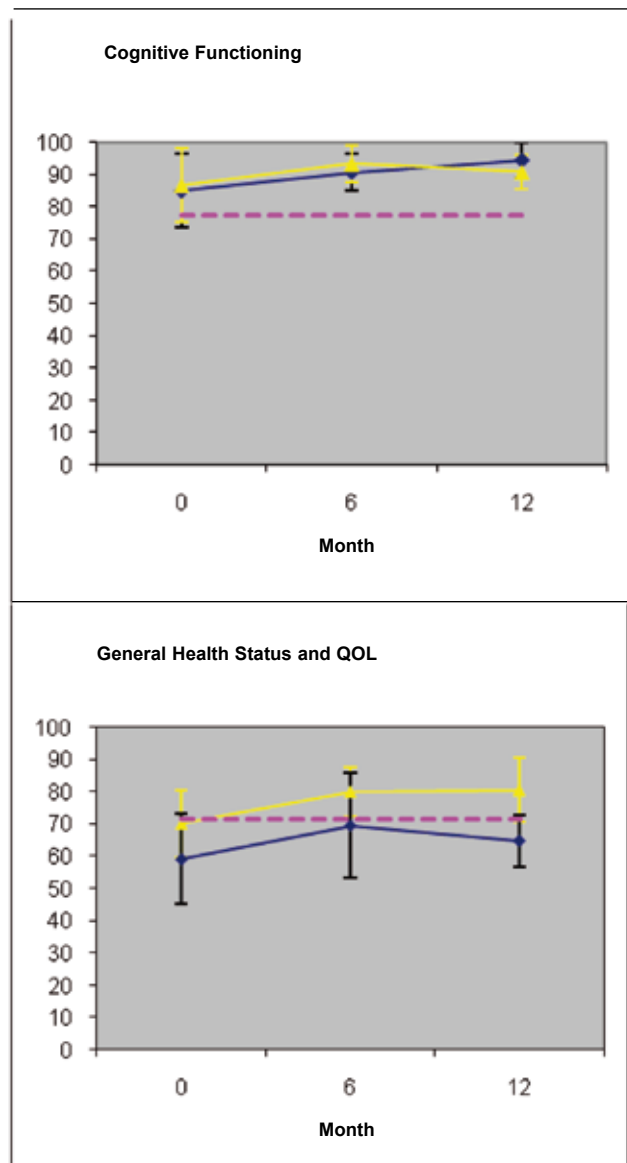


Fig. 5. Change in cognitive function and overall QOL during 12-months of transdermal estradiol therapy (EORTC QLQ-C30 and PR25 CaP-specific QOL questionnaires), the vertical bars represent means and 95% confidence intervals; yellow – locally advanced patients, blue – metastatic patients, and dotted pink – reference population.

importance. All contemporary hormone therapies are associated with significant reduction in bone mass. Bone loss of between 2.4% and 10% occurs during the first year of treatment. Further losses of between 1.4 and 2.6% occur annually for up to 10 years following androgen suppression [7, 8, 45, 46]. These losses are greater than those reported for untreated menopausal women, and are associated with high risk of osteoporotic fracture [47]. For men with untreated CaP, the accumulated incidence of osteoporotic fracture is 1%. By contrast, androgen suppression results in a 28% fracture rate after 7 years and 40 to 50% after 9 years [8]. Overall, fracture risk increases by 3.5-fold for men on conventional hormone therapies [48]. Data such as these have led to promotion of adjuvant drug therapy to protect bone density during routine patient care by the pharmaceutical industry. Bisphosphonate therapy (especially used as monthly intravenous infusions) is an additional burden to patients at substantial extra cost to health providers. Although a role for oral bisphosphonate therapy remains to be fully established, intravenous therapy is

invasive and generally limited to those with the most severe disease [46].

Estrogens (HRT) have a long established role providing osteoprotection for postmenopausal women. We have recently published preliminary evidence to demonstrate that osteoprotection is also conferred to patients with advanced CaP treated with transdermal estradiol [49]. Bone density in our series improved by 1.9 to 3.6% at one year (Fig. 4) and improved the classification of patients with bone densities in the 'at risk' range [49]. These improvements in bone density have an inherent advantage to a population already susceptible to significant skeletal morbidity (osteoporotic fracture).

#### Parenteral estrogen therapy and hot flushes

The most commonly reported side effect of conventional hormonal therapy is hot flushes. These are experienced in up to 80% of men after orchidectomy, LHRH agonists or MAB [50, 51]. In one-third of men flushes can be sufficiently severe to warrant palliation and distress is disabling in over 10% [50, 51]. The incidence of flushes and symptom severity with estrogens is far less than that caused by other hormone therapies. The SPCG-5 study reported distressing hot flushes in 37% of men treated by MAB but only 5.4% of those treated by intramuscular PEP; flushes resolved in more than 50% of the PEP group after 1 year of therapy [51]. Transdermal estrogens used in CaP men to treat symptomatic flushes from conventional hormone therapy offer complete or partial relief in up to 90% [52].

#### Parenteral estrogen therapy and gynecomastia

Gynecomastia is a well-recognized effect of estrogen by any route; severity and incidence varies from 40 to 77% [19, 20, 30]. In our study, transdermal estradiol caused mild (or less) discomfort in 63% and modest discomfort for the other 37% [26] with distress worst in the first 6 months of therapy. After this period, gynecomastia stabilized and distress decreased in most, an outcome consistent with the degree of painful gynecomastia reported for 3 mg DES therapy [19]. Pre-treatment radiotherapy as a single or 3 fraction dose can be effective in preventing gynecomastia [53]. Once gynecomastia has developed, treatment is more of a problem. Glandular proliferation, stromal expansion and periductal edema are replaced after several months by fibrosis resulting in reduced discomfort. Enlargement is then irreversible and radiation therapy at this stage has minimal impact on breast size. Gynecomastia occurs with other hormonal modalities as well, especially NSAA (in 40 to 70% where increased circulating testosterone induced by NSAA therapy is converted to estrogens within peripheral adipose tissues) [54]. As prophylactic radiotherapy or adjuvant tamoxifen are now commonly employed alongside NSAA therapy to reduce gynecomastia [55], they could equally be used in parenteral estrogen therapy.

#### Parenteral estrogen therapy and the andropause

Where there is a sudden suppression of androgens as in men treated by current endocrine therapies, a male version of andropause occurs, similar to that experienced by women during menopause. The most obvious sequelae are loss of libido and erection. Sexual function in younger patients is intimately related to testosterone levels but in the elderly, mental and psychological factors are more important meaning that distress caused to these groups may be quite different. Castration also results in decline in intellectual vitality (cognitive dysfunction) as well as complex psychological changes and a tendency to depression. Such symptoms may be far more important to patients (and their relationships) than sexual changes or hot flushes, and so should be emphasized when clinicians are counseling patients.

There is accumulating evidence of the negative effects of the andropause on QOL in men. Men with symptomatic metastases generally show improvement or stabilization of QOL parameters with short-term (up to 1 year) endocrine therapy [56, 57]. By contrast, those with non-symptomatic metastatic disease are adversely affected by androgen suppression with decreases in physical, cognitive and emotional function as well as fatigue, lethargy and depression widely reported [9, 58, 59]. Such adverse effects are most marked with LHRH agonists, especially when combined with an NSAA as MAB [60, 61] and are even more pronounced in men with early stage disease committed to long term therapy. Progressive deterioration in QOL scores is independent of the disease status, and worsens over time [10].

Parenteral estrogen may have advantage over other endocrine therapies. Epidemiological and experimental data suggest that estrogen may protect against age-related decline in cognitive function and dementia [14]. Our own data appear to support this hypothesis at least in the shorter term. Men treated with transdermal estradiol had an improved overall QOL during the first 12 months of therapy. Analysis demonstrated this to be a result of stabilized or improved functional and emotional status, reduced disease-related symptoms and minimal andropause scores. This benefit is accrued whether the patients presented with symptomatic or asymptomatic disease. Overall, scores compared favorably with those expected from the reference population (Fig. 5). It remains to be determined whether the apparent benefits of transdermal estradiol therapy continue with longer duration therapy.

#### Economic benefits of parenteral estrogen therapy

The cost of endocrine therapy for health care providers worldwide is substantial. In the USA, Medicare expenditure on LHRH agonists alone increased from \$477 million in 1994 to over \$800 million in 1999 and approaches \$2 billion annually worldwide [62, 63]. Quality-adjusted life years (QALY) analysis has revealed a cost / QALY ratio of less than \$20,000 / QALY to be universally considered as representing a reasonable use of health care resource (i.e. good value). A recent meta-analysis [62] compared the historical use of oral estrogens to orchidectomy, LHRH agonists, anti-androgens and MAB adjusting for cardiovascular toxicity of oral estrogen within the analysis. A QALY of 4.64 for oral estrogen therapy, 5.03 for anti-androgens and MAB, and 5.1 for LHRH agonists and orchidectomy was reported. The small QALY benefit of current therapies over oral estrogens (i.e. maximum of 0.46 QALY) was achieved at a huge cost. Oral estrogens cost \$8100 / QALY less than orchidectomy, whilst LHRH agonists or NSAA cost over \$100,000 / QALY and MAB \$1,110,000 / QALY respectively more than orchidectomy.

Transdermal estradiol monotherapy costs approximately one tenth the price of LHRH agonist therapy alone. This cost difference increases further when compared to combination therapy with NSAA and / or bisphosphonates. A crude estimate of the cost saving in endocrine therapy alone would amount to approximately £100,000,000 in the UK and \$900,000,000 in the USA annually [64]. More may be saved if the potential of parenteral estradiol therapy to confer long-term cardioprotective and osteoporotic benefit is also considered. Even if estrogen therapy resulted in a small reduction in the incidence of these complications, the cost savings would be considerable.

#### Conclusions and Future Directions

The recognition of the toxicity of oral estrogen concurrent with introduction of new hormone therapies led to the rapid demise of estrogen use in CaP. Little regard was given to mechanisms of toxicity and the potential to circumnavigate these. Recently, morbidity of

contemporary hormone therapies has been addressed and adjuvant therapies developed to protect against osteoporosis and andropause, but there has been little incentive to develop old treatments. As the indications for androgen suppression expand, the morbidity of current long term endocrine therapy is no longer acceptable; clinicians and health economies need to re-evaluate current as well as previous endocrine strategies.

Estrogen as a treatment for CaP is once again contemporary, evolving and exciting. Parenteral estrogen delivery appears to offer the benefits of androgen suppression with a substantially reduced cardiovascular risk. Transdermal patches are easy to apply, dose modulate and withdraw should toxicity develop. Studies on selective estrogen (and androgen) receptor modulators may provide more targeted hormonal benefits in the future and opportunities for translational research appear legion. Estrogen should still be considered in first and second line, adjuvant and salvage settings as well as in high dose treatment for men with androgen independent disease, as part of the multi modal armamentarium available to clinicians.

A phase II randomized controlled trial of transdermal estradiol compared to LHRH agonists began early 2006 in collaboration with the Clinical Trials Unit of the Medical Research Council supported by the National Cancer Research Network Prostate Cancer UK studies group and funded by Cancer Research-UK. Over 195 of the 250 men required for the initial study determining a primary end-point of cardiovascular toxicity (and secondary endpoints of efficacy using testosterone suppression and PSA levels) have been recruited. Preliminary data are promising and progression to a Phase III study is under preparation [73].

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