



Review – Prostate Cancer

Potential Benefits of Intermittent Androgen Suppression Therapy in the Treatment of Prostate Cancer: A Systematic Review of the Literature

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Abstract

Context: The well-known side-effect profile of androgen-deprivation therapy (ADT) has significant quality-of-life (QoL) implications. Intermittent androgen deprivation (IAD) alternates androgen blockade with treatment cessation to allow hormonal recovery between treatment cycles, thus potentially improving tolerability and QoL.

Objective: To evaluate available evidence regarding the efficacy and tolerability of IAD and assess its value in the treatment of prostate cancer (PCa).

Evidence acquisition: Key phase 2/3 clinical trials of IAD in PCa published within the last 10 yr were identified on Medline using the terms *prostatic neoplasms* [MeSH], *intermittent androgen suppression*, *intermittent hormonal deprivation*, *intermittent androgen deprivation*, and *intermittent hormonal therapy*. Abstracts from trials reported at 2008–2009 conferences were also included.

Evidence synthesis: Data from 19 phase 2 studies are discussed with respect to prostate-specific antigen values for treatment suspension/reinitiation, treatment regimens, cycle lengths, testosterone normalisation, and tolerability. Outcome data were promising: Most trials reported an improvement in QoL during the off-therapy periods. Interim data from eight phase 3 trials comparing IAD and continuous androgen deprivation (CAD) support the phase 2 results. IAD generally showed comparable efficacy to CAD with respect to various outcomes, including biochemical progression, progression-free survival, and overall survival. However, IAD was significantly better than CAD with respect to 3-yr risk of progression in one study, and it demonstrated tolerability benefits, particularly with respect to sexual function. Patients most likely to benefit from IAD and factors predictive of poor response are also discussed.

Conclusions: IAD seems to be as effective as CAD while showing tolerability and QoL advantages, especially recovery of sexual potency; however, there are as yet insufficient data to determine whether IAD has the potential to prevent or reverse the long-term complications associated with ADT.

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1. Introduction

Prostate cancer (PCa) is the second most common male cancer worldwide and the most frequently occurring in Europe (20.3% of the total in 2006) [1]; it is more prevalent in elderly men and increases with age [1,2]. In the United States, the number of new cases of PCa in 2007 was 218 890 and the number of deaths was 27 050 [3]. The rapid increase in the ageing population may contribute to the 16% increase in deaths from PCa reported in Europe between 1995 and 2006, despite improved detection rates [1]; however, the opposite trend has been noted in the United States and the United Kingdom [4].

1.1. Androgen-deprivation therapy

Androgen-deprivation therapy (ADT) has progressed since 1941 when surgical castration was shown to improve PCa outcomes [5,6]. Gonadotropin-releasing hormone (GnRH) agonists were discovered in 1971 [7] and are now the mainstay of PCa treatment. Single-agent treatment with GnRH agonists has produced similar survival rates to orchiectomy in advanced PCa, and adjuvant and neoadjuvant use with radiotherapy or surgery has improved survival compared with local treatment alone, especially in locally advanced and high-grade disease [8,9].

However, a potential disadvantage of GnRH agonists is the testosterone surge that can occur at the beginning of treatment if not initially given with peripheral antiandrogens. These surges, together with possible micro-surges after subsequent doses, can cause temporary symptom exacerbation and have a potentially adverse impact on long-term survival [10,11].

1.2. Rationale for intermittent treatment

A preclinical study by Bruchovsky et al [12] using the androgen-dependent Shionogi prostate cancer model demonstrated a 20-fold increase in total stem cells and a 500-fold increase in the proportion of androgen-independent stem cells on castration. It appears, therefore, that androgen suppression causes a change in stem cells from an androgen-dependent to an androgen-independent phenotype. Because this progression to androgen independence is thought to begin early after treatment initiation, stopping androgen deprivation prior to this change occurring should restore apoptotic potential and help tumour cells remain sensitive to treatment reinitiation [13–15]. In a murine model, Akakura et al [16] showed that time to progression to androgen independence was increased threefold with intermittent androgen deprivation (IAD) compared with continuous therapy.

The strategy behind IAD, therefore, is to alternate androgen blockade with treatment cessation, allowing hormonal recovery between treatment periods [10,17,18]. Treatment is continued until prostate-specific antigen (PSA) reaches a nadir, then discontinued, allowing serum testosterone to increase to normal levels; once PSA rises to a predetermined level, treatment is reinitiated [9,19,20].

The potential of IAD was investigated because the rate of diagnosis of PCa is also increasing in younger men (40–60 yr of age), meaning that hormonal therapy is being used for extended periods of time [21,22]. The well-known side-effect profile of ADT has significant quality-of-life (QoL) implications such as sexual dysfunction, hot flushes, and fatigue, and patients may develop long-term consequences such as osteoporosis, anaemia, and metabolic disorders [8,23]. Early clinical studies showed that intermittent hormonal regulation of testosterone improved QoL and reversed sexual dysfunction in patients with PCa, with no adverse impact on survival [13,24–26].

This review considers the clinical evidence supporting the effectiveness of IAD in the treatment of PCa and assesses its potential advantages over continuous therapy.

2. Evidence acquisition

A comprehensive Medline search was performed to identify key phase 2/3 clinical trials of IAD in PCa, using the search terms *prostatic neoplasms* [MeSH], *intermittent androgen suppression*, *intermittent hormonal deprivation*, *intermittent androgen deprivation*, and *intermittent hormonal therapy*. Results were restricted to the English language, giving preference to those published within the last 10 yr; abstracts from trials reported at 2008 and early 2009 conferences were also included to ensure currency of information.

3. Evidence synthesis

3.1. Phase 2 studies: methodology

The methodology of all 19 phase 2 trials included in this review are of an extremely heterogeneous design with respect to patients, PSA cut-off, cycle lengths, and treatment regimen, making comparisons difficult [27–49]. For this reason, brief study details, rather than an in-depth analysis, are given. Table 1 gives a summary of trial designs.

3.1.1. Patients

In most studies, the disease stage of populations varied. However, one study enrolled metastatic/advanced patients only [27]; one, localised only [36]; and five, a combination of localised and locally advanced [29,32,35,41,45]; three of these included mostly locally advanced patients [29,41,45], and one included mostly localised patients [32]. Patient numbers were in the range of 39–566, with only five studies including >100 patients.

3.1.2. Prostate-specific antigen cut-offs

The PSA level at which treatment was suspended was in the range 0–4 ng/ml, and most were in the region of 4 ng/ml. The PSA level at which treatment was reinitiated also varied, with the most frequent values either >10 ng/ml or >20 ng/ml. However, much lower PSA values for initiation of treatment suspension were specified in some studies for patients who had undergone prior radical prostatectomy, cryosurgery, or radiotherapy [33,35,36].

Table 1 – Summary details of phase 2 studies

Author	No.	Follow-up	Treatment	Staging	PSA (ng/ml)		No. cycles
					Nadir	Resume	
Bouchot et al [27]	43	43.7 mo (mean)	GnRH agonist (leuprolide or triptorelin) with or without flutamide	M1b	<4	>20 or Local failure or New bone metastases	1–2
Bracada et al [28]	89	34 mo (med)	Hormonal therapy	B, C, D	≈0	≈10	1–5
Bruchovsky et al [29]	103	4.2 yr (med)	Leuprolide acetate + cyproterone acetate	T1b, T2a, T2b, T3a	<4	≥10	1–5
Crook et al [31]	54	33 mo (mean)	Leuprolide + nilutamide	Recurrence after RT for clinically localised PCa or early metastatic	<4	≥10	1–5
Cury et al [32]	39	56.4 mo (med)	Buserelin acetate	T1–3	≤4	≥10	1–4
De la Taille et al [33]	146	45.6 mo (mean)	GnRH agonist + nonsteroidal antiandrogen or either treatment alone	T1–4, NXMX, N0M0, N1/M1	UD (RRP) <1 (naïve) <4 (RT)	>4 (RRP) <10 (naïve) >10 (RT)	1–8
Goldenberg et al [34]	87	65.5 mo (mean)	GnRH agonist + antiandrogen	A2, B2, C, D1, D2, recurrence after RT or RRP	≤4	10–20 (BL >20) 5–15 (BL 10–20) 4–6 (RRP)	1–5
Grossfeld et al [35]	47	24 mo (mean)	GnRH agonist + antiandrogen or GnRH agonist alone	T1c, T2, T3, T4	<0.1 (RRP) <1 (RT) <0.5 (CS) <4 (naïve)	>10 or >50% BL level or Patient request	1–5 (med 2)
Kurek et al [36]	44	48 mo (mean)	Leuprorelin acetate + cyproterone acetate	Early stages: PSA increase after RRP or with pT1b after TURP	<0.5 (RRP) <2 (pT1)	>3 (RRP) >6 (pT1)	1–4
Lane et al [37]	75	134 mo (med)	GnRH agonist + antiandrogen or GnRH agonist alone	Recurrent, locally advanced or metastatic	≤4 (or >90% of BL)	>20	1–3
Malone et al [38]	95	69 mo (med)	Leuprolide acetate + nilutamide	Stage I–IV	<4	>10 or Disease progression	1–7
Pether et al [40]	102	219 wk (mean)	GnRH agonist + antiandrogen	A2, B2, C, D1, D2, or recurrent	≤4	10–20 (BL >20) 5–15 (BL 10–20) 4–6 (RRP)	1–6
Peyromaure et al [41]	57	92 mo (med)	Cyproterone acetate or nilutamide	T2N0, T3aN0, T3bN0, T3N+	<1 or <10 if BL PSA >20	>4	1–4
Prapotnich et al [42,43]	566	81 mo (med)	GnRH agonist + nonsteroidal antiandrogen	Locally advanced, metastatic, or recurrent	<4	>20 or slope of increase >5 ng/ml over previous 3 mo	1–12
Sato et al [44]	49	136.5 wk (mean)	Leuprolide acetate + flutamide	T3N0M0, T2–T3N1M0, T4N0M0, T2–T3N0M1	<4	15 (if initial PSA >15) or BL level (if initial PSA <15)	1–4
Sciarra et al [45]	51	Group 1* 184 wk (med) Group 2† 206 wk (med)	Triptorelin + cyproterone acetate	Recurrent, clinically localised: T3a-c, T2bN0, T3aN0, T3bN0	Group 1* <0.4 Group 2† <4	Group 1* ≥0.4 Group 2† ≥4	5
Spry et al [47]	250	30 mo	Leuprolide + flutamide	Locally advanced, metastatic, locally recurrent	<4	>20 or >BL (if BL <20) or Disease progression	1–2
Strum et al [48]	52	66 mo (med)	Leuprolide acetate or goserelin + flutamide or bicalutamide or nilutamide	T1c, T2a-c, D0-2, PSAR	UD for med of 1 yr	≥5	1–2
Youssef et al [49]	74	21 mo (med)	GnRH agonist (+ antiandrogen if bone metastases)	Recurrent and/or metastatic	–	≥10	1–6 (med 3)

BL = baseline (pretreatment); CS = previously undergone cryosurgery only; med = median; GnRH = gonadotropin-releasing hormone; PCa = prostate cancer; PSAR = PSA recurrence; RRP = post-radical retropubic prostatectomy; RT = previous radiotherapy; TURP = transurethral resection of the prostate; UD = undetectable.

* Undetectable PSA following radical retropubic prostatectomy.

† No decrease in PSA below detection limit following radical retropubic prostatectomy.

3.1.3. Treatment regimens

Regimens generally used a GnRH agonist with or without an antiandrogen; the most commonly used GnRH agonist was leuprolide. Antiandrogens included cyproterone, flutamide, nilutamide, and bicalutamide, which were usually given as add-on therapy to GnRH agonist therapy.

3.2. Phase 2 studies: results

The end points of most phase 2 studies were safety and feasibility of IAD; consequently, survival data are not included in this section.

3.2.1. Cycle lengths

The number of cycles given ranged from 1 to 12, with an average of 2–3 per patient specified in four studies [29,35,39,49]. The length of time off therapy generally decreased or remained stable with each cycle (Fig. 1). A meta-analysis by Shaw et al [50] involving 10 phase 2 trials reported a median number of cycles of two per patient and a median time off therapy of 15.4 mo. Time on treatment also varied but was usually in the region of 6–9 mo [29,33,35–37,41]; Crook et al [31] identified 8-mo treatment periods with variable off-therapy intervals as a common regimen.

3.2.2. Testosterone recovery

The level of testosterone recovery was discussed in about 60% of studies [27,30–32,34,36,38,39,44,47,48]. Where reported, the proportion of men in whom serum testosterone normalised was generally high following the first cycle (in the region of 70–90%) but tended to decrease during subsequent cycles (Fig. 2; 30–32,44,48). In contrast, Bouchot et al [27] noted low levels of testosterone recovery during cycle 1; however, the authors suggested that this could be due to all patients having bone metastases and a mean age of 72 yr.

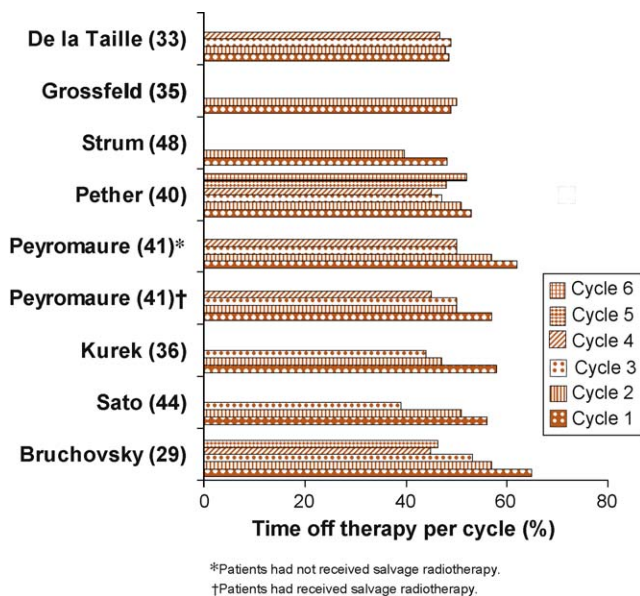


Fig. 1 – Percentage of time off therapy per cycle in patients with prostate cancer receiving intermittent androgen deprivation in phase 2 trials.

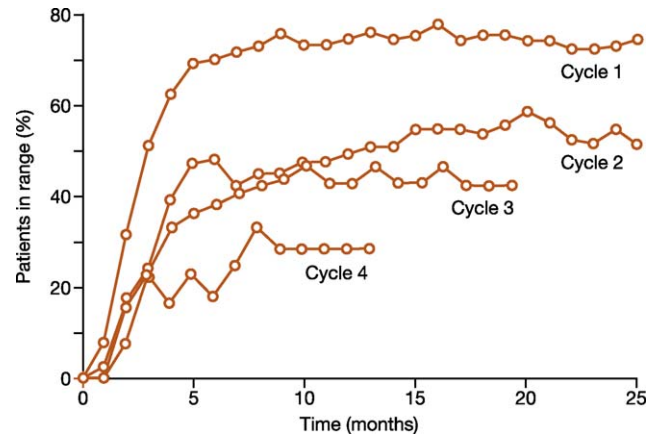


Fig. 2 – Percentage of patients with testosterone levels ≥ 7.5 nmol/l (≥ 2.2 ng/ml) following interruption of androgen deprivation therapy in patients with prostate cancer with prostate-specific antigen recurrence after radiotherapy. Reproduced with permission from Wiley Interscience [30].

Factors influencing time to delay in testosterone normalisation may include advanced age, low baseline testosterone levels, and duration of ADT [32,48,51]. Bruchovsky et al [30] also identified a close relationship between the recoveries of serum testosterone and PSA: Men who quickly recovered serum testosterone experienced a more rapid rise in serum PSA levels and a shorter time off therapy.

3.2.3. Hormone-refractory disease

Although nearly half the patients in the study by Crook et al [31] developed hormone-refractory disease (42.6%), low levels (2–16%) have been reported elsewhere [27,32,45,49]. In the Shaw meta-analysis, 181 of 1446 patients (12.5%) developed androgen independence during a maximum follow-up of 197 mo [50].

3.2.4. Tolerability and quality of life

In general, ADT was well tolerated in the phase 2 studies, with a decrease in adverse events and improvement in QoL during the off-treatment period. Malone et al [39] estimated that approximately 50% of patients recovered from anaemia during off-therapy periods and that the weight gain normally associated with ADT was offset by weight loss during off therapy because there was no net weight gain at the end of the study. Bouchot et al [27] reported hot flushes in most cases during the on-therapy period, which showed significant improvement once ADT was withdrawn. Goldenberg et al [34] observed that all patients tolerated therapy well and responded in a positive physical and psychological manner to the cycling approach.

Improvement of sexual activity was highlighted in several studies [28,34,39]. In the study by Malone et al [39], universal loss of potency occurred during the on-therapy period but was regained by 47% of evaluable patients when therapy was withdrawn. Goldenberg et al [34] reported recovery of libido and potency in men who had normal or near-normal sexual function before the start of therapy. However, in a further study, erectile function was not restored during off-therapy periods [45].

Positive effects on QoL were discussed in three studies. Bouchot et al [27] noted that pain significantly improved during on-therapy periods with no new pain occurring once therapy was withdrawn. Sato et al [44] reported significant worsening of potency and physical well-being during ADT and significant improvements in potency, lack of energy, social/family well-being, and ability to enjoy life during off-therapy periods. In a study by Spry et al [47], QoL scores also deteriorated during androgen suppression but had generally achieved baseline levels by the end of the off-treatment period. However, two studies noted no significant differences between on- and off-therapy periods for various QoL factors [27,32]; in one of these, the authors speculate that the lack of recovery of sexual activity could be explained by the small number of patients with erectile function at baseline and low testosterone levels during off therapy [27].

3.2.5. Need for phase 3 trials

Although phase 2 trials have demonstrated potential tolerability benefits of IAD in various patient groups, randomised phase 3 trials are needed to answer questions about survival, percentage of responders, and which patients are most likely to benefit from this approach. A European Organisation for Research and Treatment of Cancer (EORTC) feasibility study for phase 3 trials concluded that the concept of IAD warranted further investigation [52].

3.3. Phase 3 studies: methodology

A number of phase 3 trials are under way comparing IAD with continuous androgen deprivation (CAD), eight of which have published results [53–64]. A further trial has assessed time to testosterone normalisation following limited hormonal therapy [65].

3.3.1. Patients

Of the eight reported trials, four included patients with locally advanced disease [53,54,56–58,62] and seven with metastatic disease [53–58,60,62–64]; two specified inclusion of patients with recurrent disease [54,59,61]. The number of patients in these trials varied from 68 to 1345, but only two involved >500 patients [53,55,62]; where given, the average age of patients ranged from 66.3 to 73 yr [53–56,58,59,61,62].

3.3.2. Design

Full details of trial design are not available for all trials; five reports are available only in abstract form [56–61,64]. However, sufficient data were presented in the abstracts to allow extraction of key design features for the majority of studies, as shown in Table 2. The treatment regimen in all but one of the trials consisted of a GnRH agonist and an antiandrogen. The exception was Verhagen et al [60], in which antiandrogen monotherapy (cyproterone acetate) was the sole regimen studied.

Although there was generally consistency in the PSA levels designated for ADT discontinuation (≤ 4 ng/ml), the

criteria for resuming treatment were less uniform, with ≥ 10 ng/ml or ≥ 20 ng/ml applied to different clinical presentations. The low PSA nadir and reinitiation values used by Tunn et al [59,61] are due to the fact that the study involved patients who had relapsed after radical prostatectomy.

End points in these studies also varied to some degree; whereas the majority ($n = 5$) had time to progression as the primary end point [53,54,56–59,61,62], two assigned survival [55,64] and one focussed on QoL outcomes [60]. Average follow-up times in these studies have all been >2 yr, with a maximum of 12 yr cited by Calais da Silva et al [62].

3.4. Phase 3 studies: results

3.4.1. Cycles

Only four studies have given details of cycle length and number. Patients in the study by de Leval et al [54] underwent one to eight cycles, with 53% patients completing three or more; mean time on therapy was 3–4.7 mo, and mean time off therapy was 3.3–8.3 mo, the time decreasing with each cycle. Three cycles have been reported in the Therapy Upgrading Life in Prostate cancer (TULP) study, with mean time on therapy 6, 4.42, and 4.3 mo, and mean time off therapy 12.7, 4.98, and 0.7 mo [56,58], respectively. Two cycles were reported by Tunn et al [59,61], with mean times on therapy 6 and 5.8 mo and mean times off therapy 9.9 and 6.1 mo, respectively. The mean times on- and off-therapy in the six cycles reported by Mottet et al [63] tended to be just shorter than 3 mo (see Table 2); mean time off-therapy over 15 cycles was 49.2% per cycle [64].

Calais da Silva et al reported that patients with a PSA < 2 ng/ml spent a median of 82% of their time off therapy; overall, 50% of patients were off therapy for ≥ 52 wk and 29% for > 36 mo [62]. An update of this study in a larger cohort [53] reported 20% of IAD patients returning to therapy within 1 yr of randomisation, with 40% yet to return after 3.5 yr.

3.4.2. Prostate-specific antigen

Calais da Silva et al [62] noted that PSA was an independent predictor of progression: Levels ≥ 4 ng/ml were associated with a greater risk of progression. In an update of this study, the median times off therapy were 174 wk for patients with PSA < 1 ng/ml at randomisation and 100 wk for those with PSA 1–4 ng/ml [53].

3.4.3. Testosterone recovery

Gulley et al [65] reported that 90% of patients recovered normal testosterone levels within 18 wk following a 6-mo treatment period with a GnRH agonist; median time to recovery was 12.9 wk. In a second study in 150 patients with PSA relapse after radical prostatectomy, 91% of patients achieved normal testosterone levels after the first cycle; however, these findings were less favourable during subsequent cycles [59]. In contrast, Mottet et al [63] noted testosterone recovery in most patients during off-therapy periods, with high levels of response over the first 6 cycles and 100% of patients achieving normalisation in the 6th

Table 2 – Trial details for randomised phase 3 trials

Author	n	Primary end point	Diagnosis	Regimen (IAD vs CAD)	PSA levels (ng/ml)		Time on therapy	Time off therapy	Follow-up
					Cease treatment	Resume treatment			
Calais da Silva et al [53,62]	626	Time to subjective or objective progression	Locally advanced or metastatic; hormone naive	GnRH agonist + cyproterone acetate, 200 mg/d	<4 or ≤80% BL	≥10 (symptomatic) or ≥20 (asymptomatic) ≥20% above nadir value	–	50% ≥52 wk 29% >36 mo	51 mo (med); max 12 y
	1045						16.7 wk (median)	174 wk (med) (PSA nadir <1 ng/ml) 100 wk (med) (PSA nadir 1–4 ng/ml)	2 yr; max 7 yr
De Leval et al [54]	68	Time to androgen-independent prostate cancer	Locally advanced, metastatic or recurrent; hormone-naive	Goserelin, 3.6 mg/mo, + flutamide, 250 mg TID	≤4	≥10	1. 4.3 mo 2. 3.4 mo 3. 3.7 mo 4. 3.9 mo 5. 3.8 mo 6. 4.7 mo 7. 4.5 mo 8. 3.0 mo (mean) 7 mo (induction)	1. 8.3 mo 2. 6.3 mo 3. 6.9 mo 4. 5.7 mo 5. 5.5 mo 6. 4.9 mo 7. 3.8 mo 8. 3.3 mo (mean)	30.8 mo (mean)
Hussain et al [55]	1345	Survival	Advanced (D2); hormone naive	Goserelin + bicalutamide	≤4	–	–	–	≥75 mo
Miller et al [57]	335	Time to clinical or biochemical progression	Locally advanced (T1-4N1-3M0) or advanced (D1 or D2)	Goserelin + bicalutamide	<4 or ≥90% cf. BL	–	–	>50% for 88% patients	–
Mottet et al [63,64]	173	Overall survival	Metastatic PCa (D2) with bone metastases	Leuprorelin, 3.75 mg/mo, + flutamide 250 mg TID	<4 ng/ml	≥10 ng/ml or clinical symptomatic progression	1. 6.05 2. 2.96 3. 2.96 4. 2.93 5. 2.96 6. 2.99 (mean)	1. 3.25 2. 2.63 3. 2.83 4. 2.50 5. 2.43 6. 2.07 (mean)	–
TULP [56,58]	290	Time to clinical progression or PSA escape	Advanced or locally advanced	Buserelin depot + nilutamide	<4	≥10 (N0-3M0) ≥20 (N0-3M1)	1. 6.0 mo 2. 4.4 mo 3. 4.3 mo (mean)	1. 12.7 mo 2. 5.0 mo 3. 0.7 mo (mean)	66 mo (mean)
Tunn et al [59,61]	184	Clinical or PSA progression under treatment	PSA relapse after radical prostatectomy	Leuprorelin acetate, 3-mo depot, + cyproterone acetate	<0.5	>3	1. 6.64 mo 2. 6.43 mo 3. 6.0 mo (mean)	1. 9.36 mo 2. 5.68 mo 3. 3.6 mo (mean)	28.4 mo (mean)
Verhagen et al [60]	366		Metastatic	Cyproterone acetate, 100 mg TID	–	–	–	–	–

BL = baseline; CAD = continuous androgen deprivation; GnRH = gonadotropin-releasing hormone; IAD = intermittent androgen deprivation; max = maximum; med = median; PCa = prostate cancer; PSA = prostate-specific antigen; TID = three times daily; TULP = transurethral laser prostatectomy study.

cycle; the mean delay to normalisation was relatively consistent during all 15 consecutive cycles reported (mean: 47 d) [64].

3.4.4. Survival

In a study by Miller et al [57], about two thirds of patients receiving either IAD or CAD experienced clinical and/or biochemical progression, with no significant differences between groups with respect to median time to tumour progression (TTP) or median time to death. Similarly, Mottet et al [64] reported no significant difference between patients receiving IAD and CAD with respect to median overall survival (OS; 1265 vs 1560 d) and median progression-free survival (PFS) (620 vs 452 d). Tunn et al [59,61] also reported equivalency between IAD and CAD with respect to PFS (91.7 vs 93.6%) and median TTP (1.86 vs 2.36 yr), although estimated mean PFS was longer in the IAD group compared with the CAD group (1234 vs 1010 d). In the TULP study, median TTP was longer in the CAD arm (24.1 vs 18 mo; significance not stated); more recent data from this study show no difference in OS between groups (mean follow-up of 66 mo) [56,58]. Calais da Silva et al [62] also reported a TTP that was slightly longer, although not significantly so, in the CAD group than the IAD group (127 vs 107 d) and no significant difference in OS; updated results in a larger cohort reported equivalence for disease progression and PCa-specific deaths [53].

However, significant differences have been reported in one study. De Leval et al [54] reported that the estimated risk of 3-yr progression in CAD patients was significantly higher than in the IAD group (38.9% vs 7%; $p = 0.0052$). In patients with a Gleason score >6 , 3-yr progression rates were significantly higher in CAD than in IAD patients

($p = 0.018$) but not in patients with lower Gleason scores. Compared with CAD, the IAD group had better results with respect to the number of deaths from hormone-refractory disease (4 vs 2), number of patients with disease progression (10 vs 3), and mean TTP (21 vs 28 mo) (level of significance not stated for any outcome). In patients without bone metastases at initiation, risk of progression was significantly higher in CAD than IAD patients ($p < 0.001$).

3.4.5. Tolerability and quality of life

Early results from the study by Calais da Silva et al [62] showed no clinically meaningful differences between groups in virtually all QoL domains and no evidence that IAD carries a significantly higher risk of death. Mottet et al [64] also reported no significant difference in QoL outcomes in patients receiving IAD or CAD.

However, updated results from a larger cohort of the Calais da Silva study [53] (maximum follow-up of 7 yr; median: 2 yr) suggest a better tolerability profile for IAD versus CAD, with up to three times as many patients in the CAD arm reporting side effects compared with IAD patients (hot flushes: 23% vs 7%; gynaecomastia: 33% vs 10%; headaches: 12% vs 5%; all $p < 0.0001$). Level of sexual activity also increased in the IAD group compared with the CAD group, reported in 28 vs 10% of patients after 15 mo; Fig. 3 shows results from a larger cohort of the same study. Similarly, Miller et al [57] reported that patients' self-assessment of their overall health and sexual activity appeared to favour IAD; however, no differences in incidence of adverse events or other safety parameters were noted in this study.

Further evidence of QoL advantages comes from Verhaegen et al [60], who note that EORTC scores on physical and

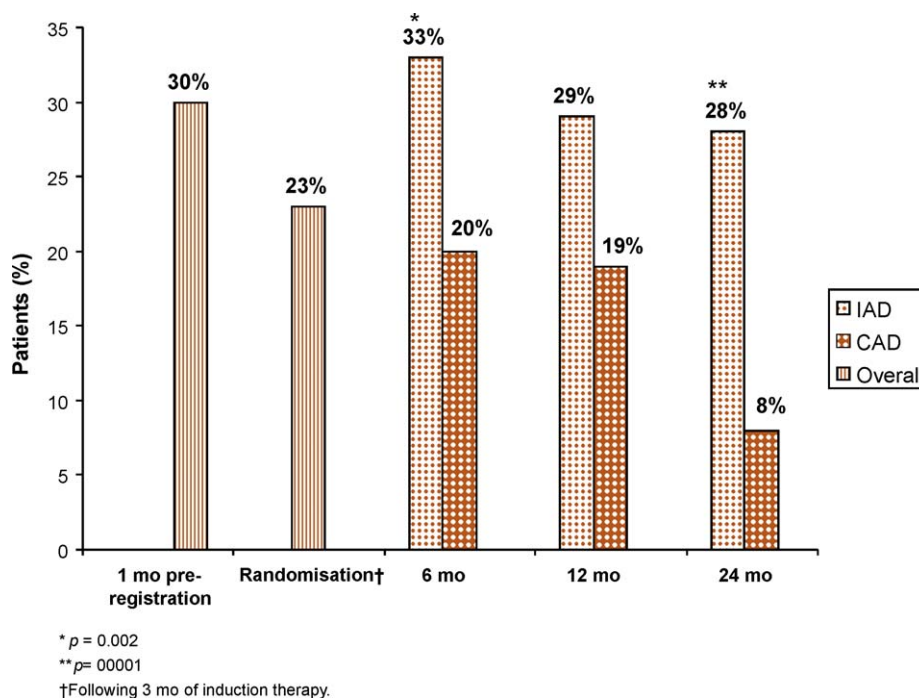


Fig. 3 – Comparison of sexual activity in patients receiving intermittent androgen deprivation (IAD) compared with patients receiving continuous androgen deprivation (CAD) in a phase 3 trial. Adapted from Calais da Silva et al [53].

emotional function were significantly better in the IAD group than in the CAD group ($p < 0.05$). Role and social function were equivalent between groups, although cognitive function was surprisingly reduced in the IAD group ($p < 0.05$) but not in the CAD group.

ADT-related side effects were reported in most patients by de Leval et al [54], most of which resolved in the IAD group on discontinuation of therapy. In the TULP study, 26 preliminary withdrawals were reported due to adverse events, 20 in the CAD group and 6 in the IAD group [56,58].

3.5. Evaluation

ADT is increasingly used in younger men and in patients with nonmetastatic disease, and many clinicians favour early versus deferred intervention [21,22]. Treatment options that potentially improve tolerability without compromising efficacy, such as IAD, are therefore to be welcomed. Although the phase 2 studies were too heterogeneous in design to allow meaningful comparison, they showed that IAD is a well-tolerated option warranting phase 3 investigation.

3.5.1. Cycle length

In the phase 2 meta-analysis, Shaw et al [50] estimated that patients spent a mean of 39% of time off therapy. On-therapy periods were more consistent than time spent off therapy and were generally in the region of 6–9 mo [66]. Data from phase 3 studies are as yet too limited to draw conclusions on cycle lengths, but times on and off therapy reported to date have been generally low: 3 to 6.64 mo and 0.7 to 12.7 mo, respectively.

3.5.2. Prostate-specific antigen levels

In both phase 2 and 3 studies, the PSA level at which treatment was suspended was usually ≤ 4 ng/ml, and reinitiation was generally either at >10 or >20 ng/ml. In several studies, lower nadir and reinitiation levels were applied to patients who had undergone radical prostatectomy [33,35,36,59,61]; reinitiation values could also vary, depending on pretreatment PSA levels or diagnosis [34,40,47,56,58]. Support for use of a reinitiation value of >10 rather than >20 ng/ml is provided by the Shaw meta-analysis [50], which showed that reinitiation at <15 ng/ml had a significantly better impact on 5-yr survival and development of androgen independence compared with reinitiation at ≥ 15 ng/ml.

In our practice, we use a PSA reinitiation point of 20 ng/ml for metastatic disease, 6–15 ng/ml in locally recurrent disease and moderately elevated pretreatment PSA levels, and <10 ng/ml for recurrences after radical prostatectomy. PSA nadir should fall to a nadir <4 ng/ml after 6 mo of therapy; however, a 9-mo on-therapy period may be required to reach maximal tissue reduction and lowest PSA levels.

3.5.3. Testosterone recovery

In phase 2 studies, positive effects were noted on testosterone levels, which were normalised in many, but

not all, patients between treatment cycles. Three phase 3 studies have supported these findings. Gulley et al [65] reported normalisation of testosterone in 90% of patients within a median of 12.9 wk following 6 mo of GnRH agonist treatment. A similar rate of recovery (91%) was reported by Tunn et al [59] after the first cycle; however, recovery rates diminished with subsequent cycles. In the third study, most patients also recovered normal testosterone levels, but the level of recovery did not diminish over 15 cycles [64].

3.5.4. Survival

Although survival was not a key end point in the phase 2 trials, Shaw et al [50] noted that patients with a period of remission of >2 yr survived longer and developed androgen independence later than those with remissions of <2 yr. Early results from phase 3 trials are limited and inconsistent. In three studies there were no significant differences in TTP [57,59,62]; in another study, TTP was longer in the CAD group than in the IAD group (significance not given) [58]. Equivalence has also been shown for cancer-specific deaths [53], OS [58,62,64], and PFS [64]. In contrast, IAD was superior to CAD in two studies with respect to 3-yr risk of progression ($p = 0.0052$) [54] and mean estimated PFS [59].

3.5.5. Tolerability and quality of life

The majority of phase 2 studies have shown IAD regimens to have promising tolerability profiles, with decreases in adverse events and improvement in QoL during off-therapy periods; this is mostly as a result of testosterone recovery eliminating symptoms of androgen suppression. Early phase 3 results also suggest a better tolerability profile and QoL with IAD than with CAD, particularly with respect to sexual function, although not all studies have demonstrated between-group differences for QoL [62,64]. In other trials where QoL was specifically measured, results favoured IAD, except for role, social, and cognitive function [57,60]. A Cochrane review commented that IAD appears to be slightly better than CAD in terms of reducing levels of impotence [67].

Of course, these early data only demonstrate the potential short-term benefits of IAD; it remains unclear whether IAD will prevent or reverse the long-term complications of ADT [8,54,66]. Because the off-therapy period is often determined solely by PSA levels and testosterone levels tend to increase along with PSA levels, patients with short off-therapy intervals derive little benefit regarding androgen-related adverse effects [66].

3.5.6. Which patients may benefit most from intermittent androgen deprivation?

Several papers discuss the type of patients who would most benefit from IAD. Crook et al [31] suggest that men with local or biochemical failures after radiotherapy would benefit from IAD because they are treatment free for longer periods of time and so are less likely to develop hormone-refractory disease. De Leval et al [54] noted that IAD was also superior to CAD in patients with poorly differentiated PCa or those without clinically apparent bone metastases. De la Taille et al [33] identified patients >70 yr of age with

localised PCa, a Gleason score of ≤ 7 , and a first off-therapy period of >1 yr as the best candidates for IAD. Grossfeld et al [35] recommend investigation of IAD in patients with clinically localised cancer who are not appropriate for definitive local treatment but have significant risk of tumour progression, patients who refuse all local treatment options despite risk of progression, and those who have failed prior local therapy.

Poor candidates for IAD have been described as those with initial bulky tumours, with numerous lymph nodes or bone metastases, PSA doubling time <9 mo, and initial serum PSA >100 ng/ml or severe pain [42,43,67]. Gleave et al [66] suggest that patients who fail to achieve a PSA nadir of <4 ng/ml after 6 mo of therapy and most men with TxNxM1 disease should not be offered IAD, whereas those with TxN1-3M0 who are sexually active, compliant, or intolerant of ADT side effects make good candidates, as long as they are informed of its investigational status.

In our experience, patients most likely to benefit are those with locally advanced PCa with or without lymph node metastases but without any evidence of bone metastases, although some patients with minimal metastatic disease could be candidates. Also, those patients with biochemical failure following radiologic or surgical therapy for PCa, those who cannot tolerate side effects of CAD, and those who wish to remain sexually active would appear to be good candidates. However, treatment should be restricted to those who can comply with close follow-up.

3.5.7. Prostate cancer treatment guidelines and intermittent androgen deprivation

Although the American Urological Association has not yet included IAD in its treatment guidelines for PCa [68], the European Association of Urology (EAU) acknowledges that IAD is at present widely offered to patients with PCa in various clinical settings and states that its status should no longer be regarded as investigational [14]. This is in contrast to the American Society of Clinical Oncology practice guidelines, which state that there are currently insufficient data to support the use of IAD outside of clinical trials [69].

The 2008 UK National Institute for Health and Clinical Excellence (NICE) recommends that IAD be offered as a first-line hormonal therapy option to men with newly diagnosed or relapsing metastatic cancer, provided they are aware of its unproven status [70]. They also note that results from uncontrolled studies have shown satisfactory outcomes and that IAD will probably be more cost effective than CAD, despite the need for close monitoring.

Irrespective of official guideline recommendations, IAD is a treatment option used worldwide by both urologists and oncologists outside of clinical trials. Urologists are comfortable prescribing potentially beneficial treatments that have limited survival data, provided there is no evidence of detrimental effects.

4. Conclusions

IAD was first proposed as a means of preserving sexual function in men undergoing treatment for PCa. In the early

1990s, Bruchovsky et al [12] demonstrated how interrupting ADT could prolong the treatment sensitivity of PCa and delay emergence of hormone refractoriness. Consequently, IAD has been a treatment option for >20 yr and the EAU considers that its status should no longer be regarded as investigational.

The data discussed here suggest that IAD will be at least as effective as CAD but with potentially better tolerability, particularly with respect to recovery of sexual potency. However, QoL data are surprisingly limited given that this, rather than survival, is the key driver for IAD and considering the length of time this approach has been under evaluation.

Based on available evidence and general clinical opinion, IAD is a valid treatment option in nonmetastatic PCa cases, that is, patients with locally advanced disease with or without lymph node involvement and those experiencing relapse following curative treatment. These patients have a higher chance of survival than those with more advanced disease, making QoL a key consideration. The fact that the NICE guidelines recommend IAD in metastatic disease reflects the ongoing controversies with this treatment option. Full results from phase 3 trials, which include both locally advanced and metastatic patients, will further clarify target populations.

IAD has come of age, and many clinicians believe it has earned its place in the management of PCa; however, there are still insufficient data to determine whether IAD has the potential to prevent or reverse the long-term complications associated with ADT. It is clear that more QoL studies using validated questionnaires are needed, as well as trials that will help us optimise treatment protocols and confirm the most suitable candidates for IAD.

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Study concept and design: Abrahamsson.

Acquisition of data: Abrahamsson.

Analysis and interpretation of data: Abrahamsson.

Drafting of the manuscript: Abrahamsson.

Critical revision of the manuscript for important intellectual content: Abrahamsson.

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