Intermittent androgen deprivation therapy for prostate cancer: translating randomized controlled trials into clinical practice

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DASON S, ALLARD CB, WANG JG, HOOGENES J, SHAYEGAN B. Intermittent androgen deprivation therapy for prostate cancer: translating randomized controlled trials into clinical practice. *Can J Urol* 2014; 21(Suppl 1):28-36.

Introduction: *Intermittent androgen deprivation therapy (IADT) for prostate cancer involves cycles of androgen deprivation therapy (ADT) with a period between cycles where testosterone is allowed to rise above castrate levels. A number of recent randomized controlled trials (RCTs) have compared survival and health-related quality-of-life (HRQOL) between IADT and continuous ADT (CADT). This review seeks to critically analyze these published trials for their relevance to clinical practice.*

Materials and methods: *Published trials were retrieved from a systematic search of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials databases using relevant keywords. Recent systematic reviews published on this topic were hand-searched for additional applicable references. The evidence was then synthesized for this review.*

Results: *A number of phase III trials have been recently published. IADT was found to be non-inferior in the primary setting for non-metastatic prostate cancer as well as in treatment of biochemical recurrence following radiotherapy. However, these studies overrepresented low risk patients in whom consideration may be given to deferred ADT rather than early treatment with IADT. In the metastatic prostate cancer setting, IADT was not found to be non-inferior to CADT. In most trials, castration related symptoms improved with IADT and overall HRQOL results were mixed. Little data are available on the effect of IADT on long term complications of ADT.*

Conclusions: *IADT remains a treatment with uncertain outcomes in metastatic prostate cancer and uncertain value over deferring ADT entirely in other prostate cancer clinical states.*

Key Words: health-related quality-of-life, cancer of the prostate, androgen deprivation therapy, hormonal therapy

Introduction

Androgen deprivation therapy (ADT) has been a mainstay in the treatment of advanced prostate cancer since its use was reported by Huggins and Hodges in 1941.[1] Androgen deprivation was classically accomplished surgically with bilateral orchiectomy. Although estrogen-mediated suppression of the hypothalamic-pituitary-gonadal (HPG)-axis has been adopted since the discovery of ADT, this approach has been limited by adverse cardiovascular effects.[2] The discovery of luteinizing hormone releasing hormone (LHRH) agonists made available a medical option for HPG-axis suppression without the thromboembolic effects of estrogens.[3] Today, medical ADT is usually favored over orchiectomy because of the potential for intermittent androgen deprivation, lack of surgical complications, and possible psychological benefits of testicular preservation.

Androgen deprivation therapy may be administered on a continuous or intermittent schedule. Continuous androgen deprivation therapy (CADT) suppresses

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testosterone to castrate levels for the duration of therapy. Alternatively, intermittent androgen deprivation therapy (IADT) involves cycles of ADT that are interrupted by injection-free intervals during which time testosterone levels are permitted to rise above castrate levels. Testosterone rises slowly during these periods and many patients will have incomplete recovery of their pre-ADT testosterone level.

The first description of IADT in clinical practice was reported by Klotz et al,[4] who reported on 20 patients with symptomatic metastatic disease treated intermittently with diethylstilbestrol (DES). Independently, Bruchovsky et al,[5] through their work with the Shionogi mouse mammary carcinoma, hypothesized that intermittent therapy could prolong time to castration resistance because CADT may preferentially enrich castration resistant stem cells.

Theories surrounding the beneficial effects of IADT prompted a number of recent phase III trials.[6] The primary hypothesis of IADT is that the testosterone rebound during treatment-free intervals of IADT may ameliorate some the adverse effects of ADT. These include castration related symptoms and their negative impact on health-related quality-of-life (HRQOL). It has also been hypothesized that IADT potentially reduces some of the bone and cardiovascular health sequelae of ADT. Finally, it has been proposed that cyclic testosterone fluctuations during IADT do not enrich cells with a castration resistant phenotype, potentially improving oncologic outcomes.[5] This review seeks to critically analyze how the available phase III trial evidence supports or refutes these theories at various prostate cancer disease states.

A disease state model of prostate cancer

Scher and Heller[7] proposed that prostate cancer may be modeled as a series of disease states through which patients may progress, ranging from localized prostate cancer to castration resistant prostate cancer (CRPC) that progresses after chemotherapy, Figure 1. Death may occur during any disease state, and therefore, does not necessarily result directly from prostate cancer due to its prolonged natural history and competing causes of death. The goals of prostate cancer therapy during any disease state include prolonging survival and optimizing HRQOL.

Prostate cancer undergoes a reduction in gland size and an increase in interglandular connective tissue during ADT.[8,9] Although residual tumor remains[9] and an inevitable progression to CRPC occurs, tumor-related symptom reduction is experienced on

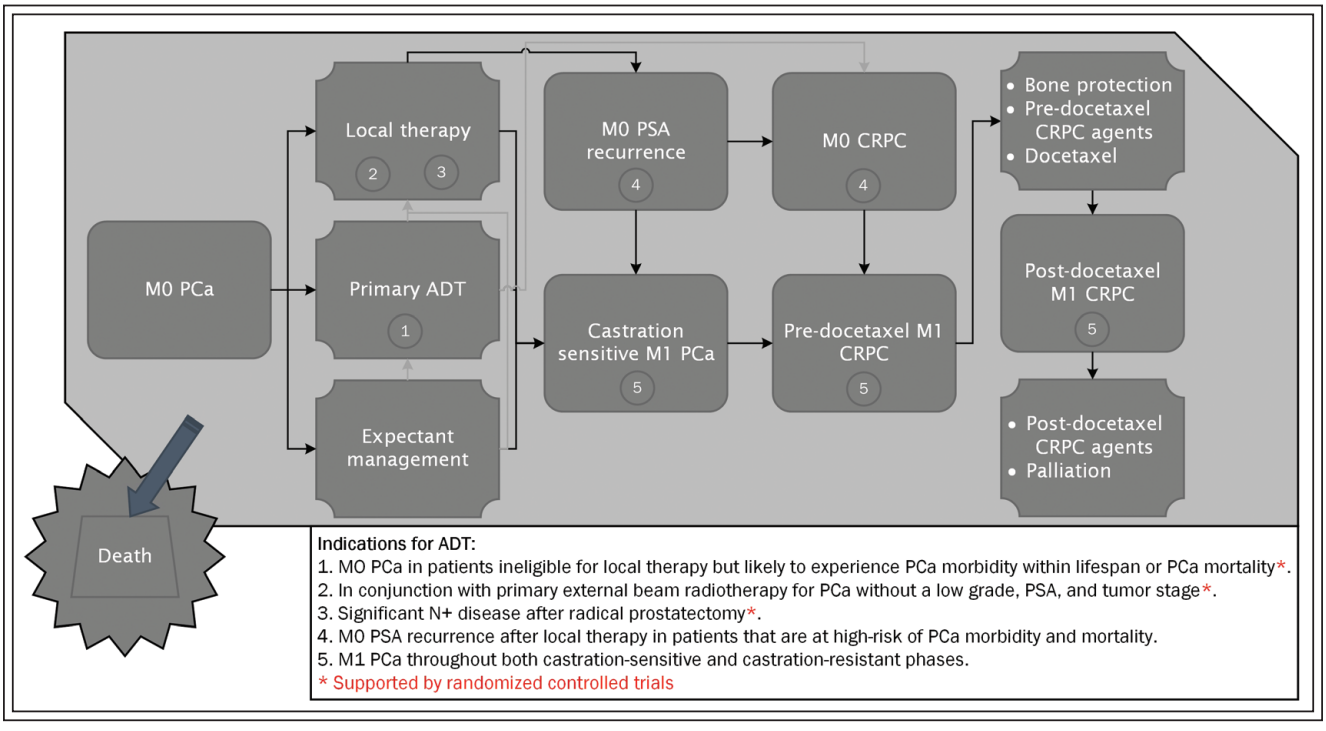

Figure 1. Indications for androgen deprivation therapy at different states of prostate cancer.[11]
PCa = prostate cancer; CRPC = castration resistant prostate cancer; ADT = androgen deprivation therapy; N+ = nodal metastases; PSA = prostate-specific antigen; M0 = non-metastatic; M1 = metastatic

initiation of ADT.[10] This effect can initially be dramatic in reducing the morbidity of symptomatic metastatic prostate cancer, including spinal cord compression, bone pain, and urinary tract obstruction. In efforts to delay the morbidity and mortality resulting from this advanced prostate cancer state, ADT is also initiated in some higher risk prostate cancer patients with asymptomatic metastases, prostate-specific antigen (PSA) recurrence after localized therapy, concurrent therapy with external beam radiotherapy, and/or patients with nodal disease after radical prostatectomy, Figure 1.[11]

Therapies for prostate cancer that are appropriate during one disease state may not necessarily be extrapolated to other disease states. As a limiting factor, the phase III IADT literature often includes heterogeneous cohorts comprised of prostate cancer patients in multiple disease states. Additionally, there is an uncertain indication for many trial patients to receive any form of ADT. This blanket approach, compounded by the publication of meta-analyses,[12,13] does not always lend itself to clinically applicable results. Multiple systematic reviews[6,12,13] thoroughly describe and tabulate the results of these phase III studies of IADT versus CADT; however, this is beyond the scope of this review. Instead, we provide suggestions for clinical practice based on a critical analysis of the IADT literature as organized by disease state, with consideration as to whether any form of ADT is indicated at all.

Primary therapy for non-metastatic (M0) prostate cancer

Local therapy is the standard of care for patients with non-metastatic (M0) prostate cancer that are not candidates for active surveillance.[14] However, given the high rates of inappropriate PSA screening,[15] a number of patients diagnosed with prostate cancer are often too old or comorbid to be candidates for local therapy. In these patients, a discussion about starting ADT is warranted when the risk of 5 year prostate cancer mortality is high.

This indication is supported by a recently published update of the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Cancers Group 30891 trial[16] which randomized patients unsuitable or unwilling to have local therapy for prostate cancer stage T0-4, N0-2, and M0 to immediate ADT (n = 492) or deferred ADT (n = 493). Only 5% of patients had known nodal metastases. Patients were followed for a median of 12.8 years with 78% of patients dying during the study, including 35% of deaths from prostate cancer and 33% from cardiovascular disease. Therapy was started in the deferred arm for new symptomatic metastases, metastases resulting in impending fracture or cord compression, pain related to prostate cancer, deterioration in performance status, and/or ureteric obstruction. Only 55% of all patients allocated to receive deferred ADT ultimately received ADT and, on average, deferred ADT required 31% of the total ADT treatment time of immediate ADT. Deferred ADT was worse than immediate ADT for time to first objective disease progression (defined as metastases or ureteric obstruction, 10 year progression rates 42% versus 30%, $p < 0.0001$). Time to castration resistant disease ADT did not differ significantly between groups ($p = 0.42$). Overall prostate cancer mortality did not differ significantly (10 year death rate of 25% versus 23%; for early and deferred ADT respectively), but overall survival was superior with immediate ADT (HR = 1.21, 95% CI 1.05-1.39, $p = 0.0085$). The authors attributed the decreased survival in the deferred ADT group to a significantly higher number of prostate cancer related deaths on deferred ADT during years 3-5 after diagnosis. PSA doubling time < 12 months served as a significant prognostic indicator of early prostate cancer death with a 3.4-fold increased risk of dying of prostate cancer with a PSA doubling time less than 12 months when compared to more than 24 months (21.0% at 5 year mortality and 46% 10 year mortality).

The EORTC 30891 trial built upon previous trials such as the Veterans' Administration Cooperative Urological Research Group (VACURG) trial,[17] which showed less progression in early ADT arms but no overall survival benefit to early ADT. The VACURG 2 trial[2] suggested a survival benefit in patients less than age 75 started on early ADT for high grade tumors. Finally, the British Medical Research Council (MRC) trial[18] of early versus deferred ADT suggested that delayed ADT was associated with more progression, complications, symptoms, and prostate cancer mortality—although there was no overall survival benefit in the final analysis.[16] The EORTC 30891, VACURG 2, and the British MRC trials can all be criticized due to inconsistent follow up resulting in an insufficient number of patients who received deferred ADT before prostate cancer mortality, bringing into question whether these trials assessed early versus no ADT instead of early versus delayed ADT.[19]

Taken together, these trials suggest that ADT may reasonably be delayed in patients ineligible for local therapy provided that patients are followed closely for disease progression. Early ADT is most beneficial in patients with more aggressive disease who are likely to

die from prostate cancer or experience prostate cancer related morbidity within their remaining years.

The most relevant IADT trial within this disease state is the South European Uroncological Group (SEUG) 9901 trial which excluded patients with prior local therapy and was comprised of 89% M0 patients.[20] A total of 918 patients were randomized to continuous or intermittent therapy with triptoreline and cyproterone acetate. At a 66 month median follow up, 525 (57.2%) of the patients had died. There was no difference in overall survival with IADT versus CADT (HR 0.90, 95% CI 0.76-1.07 – 1.21 threshold for non-inferiority).[20] The hazard ratio for prostate cancer mortality was not significantly increased with IADT.

Despite these statistical findings, it is uncertain how clinically relevant SEUG 9901 is because many patients in this trial would likely not have benefitted from any form of ADT. Approximately, 40% of patients had Gleason grade 6 or less prostate cancer and over 50% had a PSA of less than 1. This trial was not enriched with high risk patients, with only 18% of patients dying from prostate cancer between the two groups. Given such limitations, caution is still warranted in using IADT as primary therapy in patients with more aggressive disease.

Biochemical recurrence after primary therapy

There is a paucity of high quality evidence to guide which patients should receive ADT following biochemical relapse after primary therapy when there is no evidence of metastatic disease on imaging. Variables that are thought to be most important in this decision include PSA doubling time and Gleason score, as these are felt to best predict time to metastases and death.

The PR7[21] trial investigated whether IADT was non-inferior to CADT in patients who had recurred biochemically after radiotherapy. Patients with a PSA level of 3 ng/mL more than 1 year after radiotherapy for prostate cancer and no evidence of metastases were eligible for inclusion. Survival of patients in the IADT group was 8.8 years (n = 690) versus 9.1 (n = 696) years in the CADT group (HR for death 1.02, 95% CI 0.86-1.21). The trial was stopped after non-inferiority (HR < 1.25) was demonstrated at a pre-planned analysis and 524 deaths were reached (37.8%). The authors concluded that IADT was non-inferior because the HR for death was less than 1.25 and the p value for non-inferiority (HR < 1.25) equaled 0.009. In this trial, 59% of deaths were unrelated to prostate cancer and thus the authors retrospectively analyzed the data for disease-specific survival. They demonstrated a non-significant increased hazard ratio and a 7 year cumulative prostate cancer disease-related death rate of 18% and 15% in the IADT and CADT groups, respectively (p = 0.24). Time to CRPC was slightly longer in the IADT group, but the authors acknowledged that this was related to systematic biases in how CRPC was diagnosed in IADT versus CADT groups.

The PR7 trial[21] had a number of limitations in its follow up and methodology. The study group only included patients in an early clinical state of disease with a median follow up of only 6.9 years. In the National Cancer Institute's SWOG 9346,[22] a trial conducted on patients with more advanced prostate cancer, survival curves only started to separate after 5 years and 90% of patients had died after nearly 10 years of follow up. In the PR7 trial, the IADT survival curve appears to separate from CADT after approximately 9 years—without further follow up and reporting of death events, it is uncertain whether this trend would have continued. Additionally, although non-inferiority was demonstrated by the trial standards, it was defined liberally with a 1.8 year reduction in median survival required for inferiority.[22]

The PR7 trial[21] was also limited because its study population was comprised of lower risk patients. Used as a surrogate of PSA doubling time— at baseline, 78.3% of all patients enrolled in the trial had > 3 years' time since their radiotherapy. Furthermore, Gleason grade distribution was 2-6 in 42.6%, 7 in 33.0%, 8-10 in 15.2% and unavailable in 9.2%. Patients with Gleason score 8-10 disease had a 14 month poorer median survival with IADT. This poorer survival was not significant, but this was an underpowered subgroup.

The conclusion of the PR7 trial that IADT is non-inferior to CADT is thus limited to a population at lower risk of prostate cancer metastases and death. In this population, the benefit of any form of early ADT is uncertain. The PR7 trial was not appropriately designed to provide significant conclusions regarding patients most likely to experience morbidity or mortality from prostate cancer—such as those with short PSA doubling times and high initial Gleason scores. Given the limitations of this trial, IADT must be approached with caution in non-metastatic patients at risk of rapid disease progression.

Metastatic disease

For patients with metastatic disease—either on presentation or after primary therapy—SWOG 9346[22] failed to demonstrate non-inferiority of IADT. At a median follow up of 9.8 years, over 90% of the patients had died. Survival was 5.1 years in the IADT group (n = 770) and 5.8 years in the CADT group (n = 765)—

with a hazard ratio for death with IADT of 1.10 (90% CI 0.99-1.23). Prostate cancer accounted for 73% of deaths in the CADT group and 80% of deaths in the IADT group. This trial was designed such that a median survival decrease of 7 months in the IADT group was considered inferior. This required the upper limit of the 90% confidence interval to be less than 1.20 for non-inferiority, a condition that was not reached. Because the lower limit of the confidence interval included 1.0, IADT was not significantly inferior to CADT. This makes the trial statistically inconclusive, with neither the non-inferiority nor inferiority of IADT being demonstrated.

The SWOG 9346 trial performed a number of stratifications—the most interesting of which was extensive (disease in ribs, long bones, visceral organs) versus minimal disease (disease confined to spine, pelvic bones or lymph nodes). Survival with IADT versus CADT was 4.9 years versus 4.4 years (HR of 1.02, 95% CI 0.85-1.22) in the extensive disease group. However in patients with limited disease, survival was 5.4 years in the IADT group and 6.9 years in the CADT group (HR of 1.19, 95% CI 0.98-1.43). Although again statistically inconclusive—these findings suggest that caution is warranted in administering IADT for those with minimal metastatic disease.

Smaller studies with low prostate cancer mortality, mixed populations, less rigorous methodology, and shorter follow up have generally demonstrated equivalency of IADT and CADT. Since the publication of SWOG 9346, these trials may be viewed as being less significant and may therefore serve only to confound a meta-analysis.[6,23-26]

In summary, SWOG 9346 was a high quality non-inferiority trial on IADT versus CADT in patients with metastatic disease which was statistically inconclusive. IADT wasn't found to be non-inferior to CADT; but conversely, CADT was not superior to IADT. Given these inconclusive findings, CADT remains the standard of care in treatment of patients with metastatic disease.

Castration related symptoms and health related quality-of-life

Improvement in ADT-related symptomatology correlates with recovery of testosterone during off-treatment cycles which is dependent on age, baseline testosterone, number of ADT cycles, ethnicity, and the duration of induction period and length of the off-treatment period.[27] During ADT, routine testosterone measurement is currently recommended to evaluate ADT effectiveness[28] and diagnose progression to CRPC. It is also important to measure testosterone during IADT to document return of gonadal function and assess whether IADT is providing actual clinical benefit. If testosterone and symptomatic benefits are not recovered after the initial off-treatment cycles, they are less likely to return in shorter later cycles.[26] Understanding which patients will recover testosterone during the off-treatment periods is important in the decision to select IADT, particularly when employing IADT for metastatic disease, where off-treatment time is shorter (53% in SWOG 9346[22] trial versus 73% in the PR7[21] trial).

Phase III studies of IADT have confirmed patient-reported improvement in castration related symptoms during off-treatment periods as testosterone rises. Overall, study results have shown that erectile function and libido consistently improved during off-treatment periods. Hot flushes, fatigue, and headaches are also found to improve during off-treatment periods. Results concerning overall HRQOL improvements, generally measured in these trials by the multi-domain EORTC QLQ-30 questionnaire, were mixed and may relate to differences in measurement time points and in particular, blinding. Additionally, HRQOL measurement was performed with metrics not validated in this population. Unfortunately, differences in the methodology of collecting and reporting symptom and HRQOL-related data amongst phase III trials generally precluded meta-analysis of these outcomes, except for a meta-analysis of three smaller trials that reported reporting that the risk of hot flushes during IADT is lower than with CADT.[12]

In the SWOG 9346 trial,[22] patients in the IADT group received therapy for 47% of their ADT course. Reporting of HRQOL outcomes was at 3, 9 and 15 months after randomization; thereby only encompassing the first cycle off therapy. For this trial, HRQOL was divided into five domains—erectile dysfunction (ED), libido, vitality, mental health and physical functioning. Mental health, ED, and libido were improved at 3 and 9 months, vitality was improved at 9 months only and physical functioning was improved at 9 and 15 months. This equalization of HRQOL scores over time is in keeping with the fact that by the time of the 15 month analysis, 78% of men in the IADT group had resumed therapy, supporting the HRQOL benefit of IADT during off-treatment periods. HRQOL measurement in this trial was limited by a lack of blinding and the fact that that testosterone was not measured and correlated to HRQOL scores.

In the PR7 study,[21] 35% of patients had recovery of testosterone to pretreatment levels and 79% had a level of at least 5 nmol/L (144 ng/dL) by 2 years after completing the first period of treatment. Cox

regression demonstrated that men older than age 75 were less likely to return to pre-treatment testosterone level than men under age 75. Trial participants were on treatment 27% of the time. The PR7 trial authors assessed HRQOL by using a combined analysis of responses to these questionnaires at multiple fixed time points in the first 5 years of treatment. Although differences in functional HRQOL scores (physical, role, and global health) were not significant, IADT demonstrated improvements in hot flushes, desire for sexual activity, urinary symptoms and a trend towards improvement in the level of fatigue ($p = 0.07$). The functional HRQOL data in this trial is difficult to interpret because the trial was not blinded and HRQOL questionnaires were administered at fixed time points, regardless of whether IADT patients were on or off treatment.

The other smaller RCTs previously noted also generally supported improved symptomatology and sexual function during IAD. The HRQOL scores did not differ between groups in SEUG 9901,[20] although symptomatology was less frequently reported. In the FinnProstate[29] study, HRQOL scores were generally better in the IADT group in terms of activity limitation, physical capacity and sexual functioning. In the Tap 22 study,[26] which included only metastatic patients, HRQOL scores did not differ between groups, although rates of hot flushes and headache were lower in the IADT group. There was a trend towards lower rates of hot flushes in the TULP trial.[23] Improvements in hot flushes and erectile function were also suggested by de Leval et al.[24]

Long term complications of ADT

Sensitive measures of bone health outcomes were not incorporated into available phase III trials. Nonetheless, the trials did report adverse events, and fracture rates did not tend to differ. Retrospective data does support lesser bone mineral density (BMD) declines during off-treatment periods and correlates with testosterone recovery.[30,31] A recently published prospective trial analyzed the BMD declines of 56 patients on IADT without metastatic disease.[32] Patients had DEXA scans at baseline and at the start of on- and off-treatment periods. Testosterone and PSA levels were measured monthly throughout the study period. The findings of this trial demonstrated significant heterogeneity of DEXA findings but supported a decline in spine and hip BMD after the first ADT cycle and an increase in spine BMD after the first off-treatment cycle. Additionally, change in both spine and hip BMD positively correlated with testosterone levels. One post-traumatic fracture was sustained in a patient with normal BMD after a median 5.5 years follow up. This phase II trial was underpowered for the study of BMD and fractures, but does support the hypothesis that IADT may attenuate ADT-related bone loss and perhaps resultant fractures. Because testosterone recovery and off-treatment intervals are greatest when IADT is applied for non-metastatic low risk disease, if ADT is to be employed at all, this beneficial effect on bone health may be particularly significant in these patients. However, IADT may result in an increase in skeletal-related events in metastatic patients should treatment not be resumed early enough. Ultimately, bone health in the ADT population may be more readily improved by basic interventions such as periodic DEXA scans, mitigating aggravating life-style behaviors, calcium and vitamin D supplementation, and treating osteoporotic or osteopenic patients, all of which are largely underutilized by surveyed Canadian practitioners.[33]

Although ADT promotes cardiovascular disease,[11] conflicting evidence exists for its effects on cardiovascular death.[34] The use of GnRH antagonists instead of agonists may have a beneficial impact on 1 year cardiovascular events.[35] High quality data are lacking to support the effect of IADT on cardiovascular health. In adverse event reporting for published phase III trials, cardiovascular events did not significantly differ; but these trials were underpowered for these outcomes and did not describe cardiovascular risk demographics of included patients. In particular, both the SWOG 9346 and PR7 trials did not find differences in cardiovascular events.[21,22] In the SEUG 9901 trial,[20] there were 107/462 (23.2%) cardiovascular deaths in the IADT arm versus 122/456 (26.8%) in the CADT arm, but this difference was not significant. Benefits of IADT on other long term effects of ADT,[11] like mood, cognition, metabolic syndrome, acute kidney injury,[36] anemia, and stroke are also uncertain.

Summary and clinical protocol

Survival-related outcomes for IADT have been compared to CADT in a number of recent phase III trials. Local therapy or active surveillance are the standards of care for patients with M0 prostate cancer,[14] while watchful waiting with deferred ADT is appropriate for select patients with reduced life expectancy. If early primary ADT is to be administered due to higher risk prostate cancer in a patient with a reduced life expectancy, caution is warranted in administering IADT. Higher risk prostate cancer

patients were underrepresented in the SEUG 9901[20] trial which concluded non-inferiority of IADT to CADT in this prostate cancer state. Similarly, for patients with biochemical relapse after radiotherapy, there is no evidence that early ADT in lower risk relapsing patients is beneficial—and higher risk patients were a minority population of the PR7 trial,[21] which found non-inferiority of IADT to CADT in this prostate cancer state. In patients with metastatic disease, CADT remains the standard of care as SWOG 9346[22] was statistically inconclusive, finding neither the non-inferiority of IADT to CADT nor the superiority of CADT to IADT. Although meta-analyses of IADT have been published,[12,13] this approach has limited clinical relevance as it combines results from separate prostate cancer disease states and contaminates the results of very high-quality trials with low-quality trials.

Castration related symptoms including ED, low libido, hot flushes, fatigue, and headaches are improved by IADT during off-treatment periods. This likely relates to improvements in testosterone during off-treatment periods although a placebo effect remains a possible contributor.

If symptom management is unsuccessful, consideration should be given as to whether watchful waiting and deferred ADT is an appropriate option for these patients at this state of his disease—namely the patient receiving primary ADT or ADT for biochemical relapse following local therapy. If some form of ADT is still felt to be necessary, IADT has an indication here as a compromise between uncertain survival outcomes in higher risk patients and improved symptomatology.

Although there are small variations in how IADT is applied amongst phase III trials, the general principles are the same, Figure 2. As illustrated in Figure 2, IADT begins with an induction period of ADT administration. This period may be as short as 3 months (as seen in the SEUG 9901 trial, or as long as 8 months as in the PR7 trial). If, after the induction period, PSA is suppressed adequately (4 ng/mL in SWOG 9346, PR7, and SEUG 9901) then ADT administration may be halted. Prostate specific antigen levels and clinical status are closely followed, with ADT resumed on certain triggers such as symptoms or a PSA rise to 10-20 ng/mL (10 ng/mL in PR7, 20 ng/mL or baseline in SWOG 9346 and 20 ng/mL in SEUG 9901). If PSA is again suppressed to 4 ng/mL or less

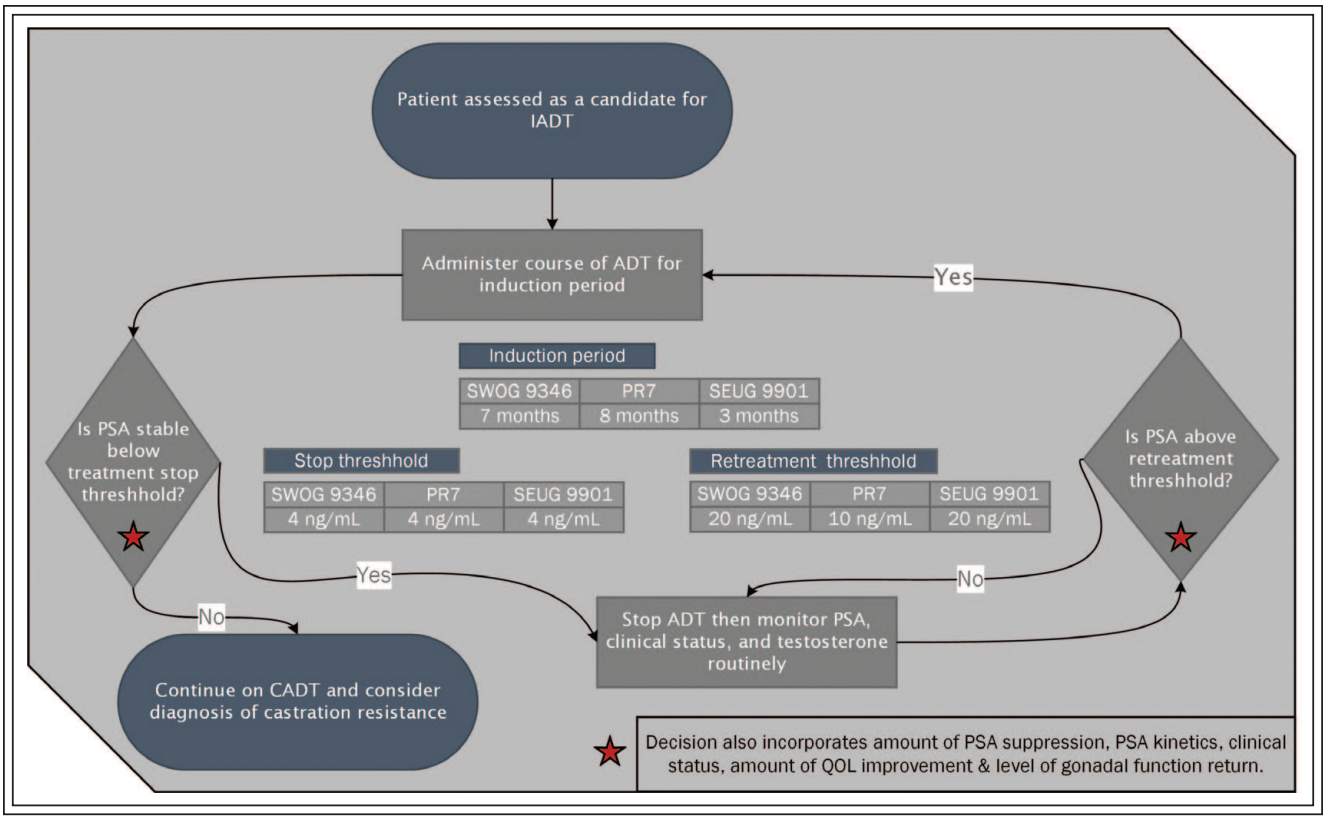

Figure 2. Clinical protocol for intermittent androgen deprivation therapy administration.
ADT = androgen deprivation therapy; IADT = intermittent ADT; CADT = continuous ADT; PSA = prostate-specific antigen. SWOG 9346, PR7 and SEUG 9901 are the three largest phase III trials comparison IADT and CADT.

TABLE 1. **Follow up of non-urologic androgen deprivation therapy complications. Modified from Grossman and Zajac.[37]**

COMPLICATION	RECOMMENDATIONS
Metabolic and cardiovascular complications	**Routinely assess:** • BMI, waist circumference, blood pressure • Screening for anemia, glucose intolerance and dyslipidemia **Manage:** • Lifestyle interventions including smoking cessation, exercise and dietary modification • Medications for control of blood pressure, diabetes and dyslipidemia
Skeletal complications	**Routinely assess:** • Risk factors for osteoporosis • Osteoporosis fracture risk stratification with tools such as FRAX (http://www.shef.ac.uk/FRAX/tool.aspx?country=19) • Assess falls risk • Measure serum calcium, creatinine, vitamin D, liver function and TSH • Measure bone mineral density with DEXA. Thoracolumbar spine x-rays in men with osteopenia (T-score <-1.5) **Manage:** • Lifestyle interventions such as smoking cessation, limiting alcohol intake, and weight-bearing exercises • Supplement calcium (1200 mg elemental calcium) and vitamin D (800 IU) intake • Treat appropriate patients with bisphosphonates or denosumab based on DEXA T-score, estimated osteoporosis fracture risk (FRAX) and history of fragility fracture

DEXA = dual energy x-ray absorptiometry

after another cycle of ADT, ADT may be halted again and the process repeated. Progression occurs when PSA or symptomatology is not suppressed by a full cycle of ADT and these patients should be considered to have CRPC. It is uncertain whether outcomes are different when a LHRH agonist or antagonist are used and whether there is benefit in adding a non-steroidal antiandrogen for combined androgen blockade. The role of LHRH antagonists in IADT are being currently examined in multiple clinical trials.

As with CADT, IADT warrants a proactive approach to ADT-related complications. Cardiovascular, metabolic, and bone complications that are ADT-related are similar to those experienced by the general population and familiar to primary care physicians. Accordingly, prescribers of ADT should ensure that patients are also following up appropriately with their primary care physicians for the diagnosis, treatment, and prevention of these complications. Grossman and Zajac[37] have suggested some ways that ADT patients should be monitored and treated with respect to these complications, Table 1. Knowledge transfer and careful care coordination with primary care physicians is needed to facilitate the comprehensive care required by patients receiving ADT.

Disclosure

The authors have no potential conflict of interest. □

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