Managing prostate cancer: the role of hormone therapy

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RAMIREZ ML, KEANE TE, EVANS CP. Managing prostate cancer: the role of hormone therapy. The Canadian Journal of Urology. 2007;14 (Supplement 1):10-18.

Androgen deprivation therapy has been the mainstay of treatment for men with metastatic prostate cancer and now plays a more active role in the management of less advanced cancers as neoadjuvant and adjuvant treatment. Investigative uses include primary therapy for patients unsuitable for definitive therapy and as a complement to ablative procedures, brachytherapy, and chemotherapy. Intermittent androgen deprivation therapy is being considered as an alternative to continuous therapy and further evaluated as triple androgen blockade in conjunction with finasteride. Many accepted and potential management schemes incorporating hormonal therapy are increasingly employed despite indeterminate indications for use. Here, we review currently available data on the efficacy of hormonal therapy with regard to complete androgen ablation, primary, neoadjuvant, and adjuvant therapy. Additionally, we examine the usefulness of delayed versus immediate administration, intermittent androgen deprivation, and other prospective applications for hormonal therapy.

Key Words: hormonal therapy, neoadjuvant therapy, adjuvant therapy, intermittent androgen deprivation, prostate cancer

Introduction

Approximately 20% of men with newly diagnosed prostate cancer (CaP) will present with advanced or metastatic disease.[1] Treatment in these men aims to prolong survival and improve quality of life. Since Huggins and Hodges demonstrated malignant prostate cells respond to hormonal manipulation,[2] androgen deprivation therapy (ADT) has been the standard systemic therapy for men with advanced disease. The role of ADT has now extended beyond palliative care to include less advanced patients treated concurrently with surgery or radiation. Data from CaPSURE reveal that the use of ADT is increasing in primary and adjuvant therapy across all treatment types and risk groups, with the highest increase in prevalence detected in neoadjuvant treatment to radiotherapy,[3] Figure 1.

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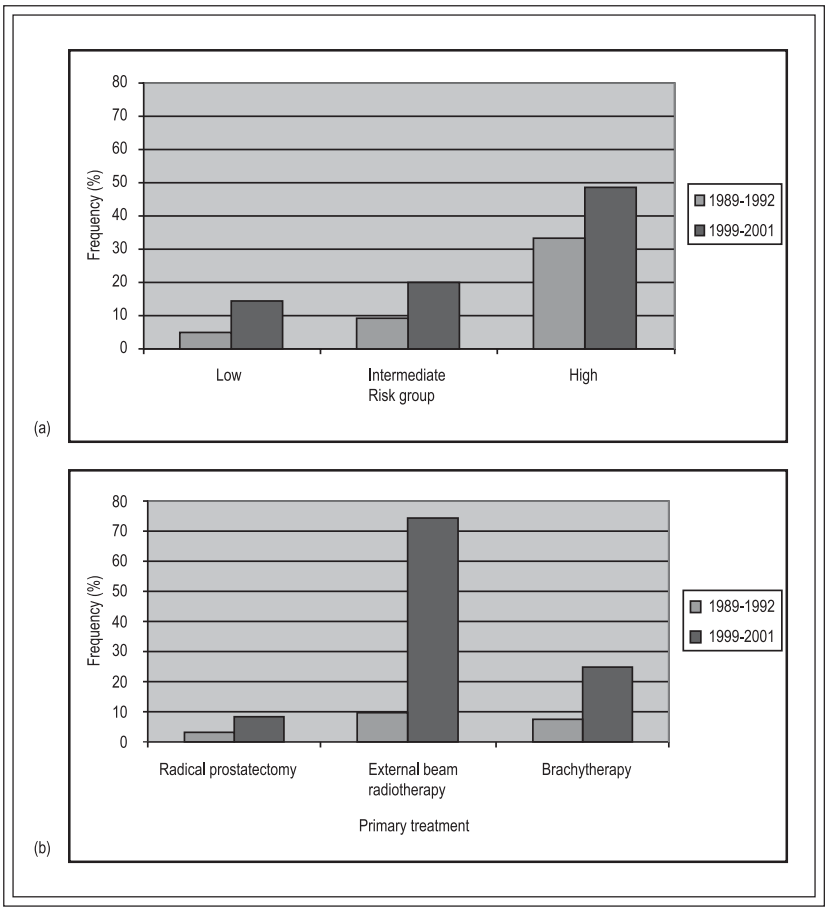

Figure 1. Analysis from 7195 patients on CaPSURE comparing trends from 1989-1992 to 1999-2001 in a) overall use of primary ADT, stratified by prostate cancer risk group and b) use of neoadjuvant ADT stratified by primary treatment type. Data from Cooperberg et al.[3]

Recognizing the absence of a definitive controlled trial, the prevailing opinion is that hormonal therapy improves disease-specific survival in metastatic CaP. However, indication for ADT as primary, adjuvant, or neoadjuvant therapy for earlier stages of CaP, as well as the timing and duration of administration in advanced CaP, are areas currently under investigation. Crucial issues for appropriate management include recognizing the most effective duration of therapy which yields the least morbidity and whether early therapy is superior to deferring treatment until clinical progression. Moreover, to minimize the side effects of androgen withdrawal and delay progression to an androgen independent state, intermittent androgen deprivation (IAD) has been evaluated as an alternative to continuous administration.

ADT for early CaP has demonstrated an improvement in clinical and pathological variables, but not a consistent gain in overall survival. Disparities in survival outcomes between various patient populations add further complexity. The appropriate role of hormonal therapy needs to be better defined to ensure treatment goals are met for individualized patients. Differences in efficacy may exist between individual therapeutic agents; however, this will not be addressed here. The objective of this overview is to present the benefits and limitations of hormone therapy as neoadjuvant, adjuvant, and primary treatment in the management of prostate cancer. Conventional, alternative, and experimental hormonal strategies will also be discussed.

ADT therapies

Complete androgen ablation

Complete androgen ablation (CAB), the combination of androgen suppression and antiandrogens, is believed to impart an advantage over androgen suppression alone. Numerous randomized trials comparing the two approaches reveal a significant survival benefit, but with minimal certainty. A Prostate Cancer Trialists' Collaborative Group (PCTCG) meta-analysis of 27 trials has examined mortality outcomes in over 8000 men, 88% with M+ disease.[4] Inclusion criteria included the administration of CAB for at least 1 year, androgen suppression achieved by orchiectomy or a long-term luteinizing hormone-releasing hormone (LHRH) agonist, and the addition of flutamide, nilutamide, or cyproterone acetate as antiandrogen therapy. CAB with nilutamide or flutamide offered an age-independent 2.9% increase in survival at 5 years ($p = 0.005$, 95% CI 0.4-5.4), while CAB with cyproterone acetate had a 2.7% survival disadvantage ($p = 0.04$).

This advantage was evident despite several limitations which may have undermined any potential survival benefit: many of the trials were underpowered and could never have shown the differences expected; the majority of patients had bony metastatic disease, much more advanced than normally seen today; and many patients were continued on CAB despite progression, since the effects of androgen withdrawal were unknown at the time. Moreover, no effective chemotherapy was available and the 2.9% survival advantage was an average, i.e. some patients received no benefit while others may have survived an additional

9-10 months. Currently, we have no way of identifying who will or will not gain from CAB; therefore, it may be acceptable to offer CAB routinely.

An exploratory analysis of a double-blind, placebo-controlled phase III study evaluated the efficacy of CAB in 99 Japanese patients with stage C disease.[5] Bicalutamide was administered as antiandrogen therapy and dosed at 80 mg/day, which is comparable to the 150 mg/day dosage given in the United States in terms of body mass. At a median observation period of 144 weeks, time to progression was significantly longer in patients who received CAB as opposed to those receiving LHRH monotherapy ($p < 0.01$). After stratification by age, PSA level at diagnosis, and tumor differentiation, CAB maintained superior efficacy. Patients in this trial with stage D disease also benefited from CAB, with similar survival outcomes to those reported by PCTCG. CAB has thus become a rational approach to hormonal therapy, although the costs and side effects are often reasons that some providers do not use it in individual patients.

Neo-adjuvant therapy

Laboratory research indicates that ADT suppresses tumor burden via apoptosis, reduction of distant microscopic tumor foci, and inhibition of malignant cell growth within the prostate.[6] Clinically, a decrease in tumor bulk prior to local therapy may improve locoregional control, and in the case of surgical treatment, increase the chance of cure if negative surgical margins can be achieved. Though data demonstrate a reduction in the rate of positive surgical margins with neoadjuvant ADT (NADT), it seems to have no effect on the incidence of seminal vesicle invasion and lymph node metastasis. Several studies have therefore assessed whether NADT ultimately translates into longer time to progression or increased survival.

Soloway et al conducted a multi-institutional prospective trial of 303 patients with stage cT2b prostate cancer randomized to receive radical prostatectomy with or without 3 months of leuprolide plus flutamide.[7] Although NADT resulted in a significant decrease in positive surgical margins and urethral margin involvement, there was no difference in seminal vesicle involvement, positive lymph nodes, or PSA recurrence at 5 years, regardless of Gleason score.[8] A similar prospective study of 126 patients with cT1b-T3aNXM0 validates that there is no survival advantage in using a 3-month course of NADT prior to radical prostatectomy.[9] Despite a decrease in positive surgical margins with the addition of NADT, the two groups were found to have comparable progression-free and overall survival rates at 7-year follow-up. In addition, data reveal that the duration of hormonal treatment does not seem to be a factor influencing survival. A randomized, comparative study of 547 men receiving either 3 months or 8 months of NADT preceding radical prostatectomy showed no difference in PSA recurrence at 48-month follow-up ($p = 0.4225$).[10]

In contrast, NADT has shown a survival benefit for select patients undergoing external beam radiation therapy (XRT). The Radiation Therapy Oncology Group 86-10 phase III trial randomized 471 patients with cT2-4NXM0 disease to receive 4 months of ADT initiated 2 months prior to XRT or XRT alone.[11] Analysis at 8 years revealed androgen deprivation was associated with an improvement in local control, reduction in the incidence of distant metastases, and increased clinical and biochemical disease-free survival, defined as PSA < 1.5 ng/ml, Table 1. Subset analysis demonstrated an overall survival benefit only in patients with Gleason 2-6 disease. With bulky tumors, cytoreduction before radiotherapy seems to provide valuable long-term tumor control.

TABLE 1. **RTOG 86-10 outcomes at 8 years from 471 patients randomized to RT or RT with 4 months of neoadjuvant ADT. Adapted from Pilepich et al.[11]**

	RT	RT + ADT	p-value
Local control (%)	30	42	0.016
Distant metastases (%)	45	34	0.04
Disease-free survival (%)	21	33	0.004
bNED (%)	10	24	< 0.0001
Overall survival* (%)	70	52	0.015

*Gleason 2-6 subset
RT = radiotherapy; bNED = biochemically no evidence of disease

Further studies have evaluated whether longer hormonal treatment provides any additional benefit to radiotherapy. Crook et al report the results of a multicenter phase III randomized trial of 3 months versus 8 months of NADT in patients with clinically localized CaP.[12] At 3 years follow-up, disease-free survival and types of failure (biochemical, local, and distant) were comparable in the two arms. High-risk patients (stage T3, GS 8-10 or PSA > 20ng/ml) showed improvement with longer treatment periods, but statistical significance was not reached. A large-scale randomized trial (RTOG 99-10) is currently underway to assess the optimal duration of NADT.

Common practice has been to downsize large prostates with ADT prior to brachytherapy, potentially decreasing toxicity and enhancing dosimetry. Few studies have evaluated whether the addition of ADT offers a survival advantage to the patients. In a large retrospective study, 163 patients with clinically confined CaP and prostate glands ≥ 60g underwent treatment for a median of 3.4 months before brachytherapy.[13] After matched-pair analysis to those not receiving neoadjuvant therapy, no difference was found between 5-year PSA recurrence-free survival rates (86.9% versus 87.1%, p = 0.935). Further subgroup analysis stratified by Gleason score, pretreatment PSA, and disease stage failed to demonstrate any significance. Likewise, lack of data showing a survival benefit for NADT with cryosurgery limits the role of ADT to enlarged prostates that require cytoreduction for effective local therapy.

Adjuvant therapy: immediate versus delayed

Hormone management in conjunction with definitive treatment for locally advanced CaP has been studied extensively and shown to impart a significant survival benefit following both radical prostatectomy and radiotherapy, yet controversy exists over the appropriate timing of hormone administration. Data from Messing et al support the use of immediate antiandrogen therapy after radical prostatectomy and pelvic lymphadenectomy in patients with node-positive disease. Ninety-eight patients were randomized to receive either immediate antiandrogen therapy (goserelin or bilateral orchiectomy) or observation until clinical progression.[14] A central histological review was conducted to regrade Gleason scores for an update at a median follow-up of 11.9 years. As in the initial analysis, overall, cancer-specific, and recurrence-free survival remained significantly better among men who received immediate adjuvant therapy as opposed to those who received initial observation.[15] A recent matched-cohort analysis of over 6000 patients undergoing radical prostatectomy for node-positive CaP further substantiates the improvement in 10-year cancer-specific and systemic progression-free survival with adjuvant ADT.[16] Moreover, this survival advantage tended to decrease as ADT was administered further along in the disease process. Patients who underwent delayed ADT at PSA ≥ 2.0 ng/ml had significantly worse outcomes than those receiving immediate treatment. Multivariate analysis demonstrated ADT had no impact on survival in patients with systemic progression.

Numerous prospective, randomized trials have validated the use of ADT in high-risk patients treated with definitive radiotherapy.[17-19] RTOG 85-31 randomly assigned patients to receive XRT followed by long-term goserelin or XRT with subsequent hormonal intervention only in the event of relapse.[19] At a median follow-up of 7.6 years, the adjuvant arm benefited in regards to local and distant failure rates, PSA progression, overall survival rate, and cancer-specific mortality, Figure 2. In multivariate analysis adjusting for Gleason score, nodal

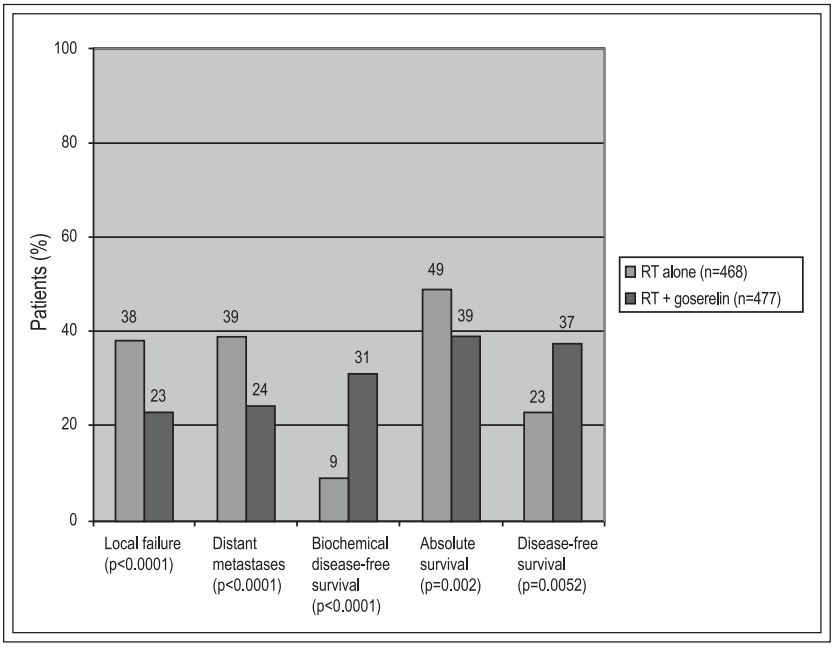

Figure 2. Results of RTOG 85-31. Data are from 945 patients randomized to receive radiotherapy or radiotherapy with adjuvant goserelin. The addition of ADT significantly improved all endpoints (10-year estimated). Data from Pilepich et al. [19]

TABLE 2. **RTOG 92-02 results: 5-year rate outcomes for 1554 patients treated with radiotherapy and either short-term or long-term hormonal therapy. Data from Hanks et al.[23]**

	XRT + ADT for a duration of 4 months	28 months	p value
Disease-free survival (%)	28.1	46.4	< 0.0001
Local progression (%)	12.3	6.4	0.0001
Distant metastases (%)	17.0	11.5	0.0035
Biochemical failure (%)	55.5	28.0	< 0.0001
Cause-specific survival (%)	91.2	94.6	0.006

*Gleason 8-10 subset only

involvement, and clinical stage, treatment remained statistically significant in favor of the adjuvant arm for all endpoints. The European Organization for Research and Treatment of Cancer (EORTC) 22863 evaluated 415 patients with T1-2 grade 3 or T3-4 N0-1M0 CaP.[20] Patients were randomized to XRT or XRT plus 3 years of goserelin. At a median follow-up of 66 months, a significant survival benefit was seen for low, intermediate, and high risk patients who received concomitant ADT.[18] While a limitation of these studies is the lack of a hormone therapy control group, the data are impressive and mandate the use of adjuvant ADT in locally advanced CaP.

Data from retrospective analyses demonstrate that the risk of cerebrovascular and cardiac events[21] and cardiac mortality[22] rises with increased duration of ADT. Shorter duration of therapy has therefore been investigated in an effort to reduce the cost and side effects of androgen deprivation, but results fail to show equivalent efficacy to more extensive therapy. RTOG 92-02 compared long-term versus short-term adjuvant therapy in combination with XRT.[23] Patients with cT2c-T4 disease received goserelin and flutamide beginning 2 months prior to radiotherapy and continuing for either 4 or 28 months. At 5.6 years, all endpoints except overall survival were significantly better in men receiving long-term androgen suppression, and subset analysis revealed an overall survival advantage in patients with a Gleason score of 8-10, Table 2. EORTC 22961 was designed to demonstrate similar survival in patients who receive 6 months of combined adjuvant ADT as in patients with 2.5 years of treatment.[24] However, at 5.2 years median follow-up, results reveal differences in progression-free, disease-free, and overall survival favoring long-term ADT, Table 3. Most patients had T2c-T3N0 disease, and data were not available when risk stratified by Gleason score. Thus, it is unknown whether patients at intermediate risk may in fact benefit equally from a shorter duration of therapy.

Primary therapy

Initially, primary ADT was reserved for those patients with metastatic disease. However, in patients unsuitable for definitive therapy, ADT is now suggested as a treatment option that may confer a survival advantage in certain patients. EORTC trial 30891 examined the effects of immediate versus deferred ADT in 985 patients with newly diagnosed T0-4N0-2M0 who either refused definitive treatment or were deemed unsuitable.[25]

TABLE 3. **EORTC 22961 5-year survival data from 970 patients treated with radiotherapy and either short-term or long-term hormonal therapy. Data from Bolla et al.[24]**

	Adjuvant ADT for a duration of 6 months (n = 483)	36 months (n = 487)	HR
PSA-PFS (%)	58.9	78.3	2.29 (98.2% CI: 1.81-2.90)
Clinical-PFS (%)	68.9	81.8	1.93 (98.2% CI: 1.49-2.51)
Ocerall survival (%)	80.6	85.3	1.43 (96.4% CI: 1.04-1.98)

PSA = prostate specific antigen; PFS = progression free survival

Median age at randomization was 73 years. At a median follow-up of 7.8 years, 55% of patients had died, mostly of CaP (35.7%) or cardiovascular disease (34.2%). Overall survival favored immediate treatment due to fewer deaths from causes other than CaP (HR 1.25, 95% CI 1.05-1.48). No difference in CaP death was found between arms, but the relatively small number of events was statistically limiting (n = 193). Moreover, results indicate significantly more pain, higher risk of pathologic fracture, and obstruction necessitating TURP in the deferred arm, while significantly more ADT side effects were present in the immediate treatment arm. Further subgroup analysis was recently conducted to determine which patients were at risk to die from CaP.[26] Patients with PSA > 50 ng/ml and/or a PSA doubling time ≤ 12 months were at increased risk of cancer-specific death and profited most from treatment. The investigators recommend immediate ADT for these high risk patients, though further exploration is needed to substantiate these results.

Expanding uses of ADT

Intermittent androgen deprivation

Based on results of animal experiments, the concept of IAD suggests that exposing surviving stem cells to androgens delays development of androgen-insensitive survival mechanisms via a conditioning effect. Recently, IAD administration has been shown to result in significantly less increase in chromogranin-A, a marker of neuroendrocrine differentiation that plays a role in progression to androgen independent prostate cancer.[27] Clinical use of ADT aims to delay progression to the hormone refractory state, induce multiple apoptotic tumor regressions, improve patient quality of life with drug holidays, and reduce the cost of therapy.

A few prospective, randomized studies have assessed the feasibility of IAD. A recent trial evaluated 335 men with D1/D2 disease randomized to either continuous (CAD) or IAD with goserelin and bicalutamide.[28] Of those on IAD, 88% were off therapy 50% of the time. A trend towards better well-being and sexual function existed in men on IAD, with a median time to progression of 16.6 months as compared to 11 months in men on CAD. However, none of these differences reached statistical significance, and no benefit was demonstrated with regards to overall quality of life or survival.

A randomized, prospective phase III trial comparing IAD to CAD in 167 patients with PSA relapse after radical prostatectomy demonstrated no significant difference with regard to androgen-independent progression.[29] However, improved quality of life and lower incidence of hyperhydrosis in the IAD arm promote its use as an alternative option. Another advantage to IAD may be reduction in bone loss. Machado et al evaluated the incidence of osteoporosis in 44 nonrandomized patients receiving IAD or CAD.[30] In both groups, half the patients developed osteoporosis. Compared to 50% of patients on CAD, 70% of patients on IAD regained bone mass, characterized by osteopenia or normal DEXA scan during the 3-year follow-up.

While IAD appears to offer certain advantages, is an approach that remains experimental until long-term survival and quality of life data are assessed. SWOG 9346, an ongoing phase III trial designed to determine whether survival with IAD is equivalent to survival with CAD, will substantiate current data. Figure 3 presents an outline of the SWOG treatment protocol, which uses established methods of stopping and restarting therapy as per predetermined PSA levels.

Alternative ADT strategies

Others have proposed IAD in combination with chemotherapy may delay the onset of androgen independence, given the volume of systemic disease and occult hormone-refractory cancer cells in advanced and/or metastatic disease. A preliminary report of 41 patients on combined IAD and weekly docetaxel administered for 4-5 monthly cycles demonstrated a 92.6% disease-specific survival at a median follow-up of 42 months.[31] A comparison study of chemotherapy-based androgen deprivation with ADT alone has yet to be elicited.

Another approach to managing CaP employs triple androgen blockade (TAB), consisting of induction with a LHRH agonist, an antiandrogen, and intracellular androgen deprivation via daily finasteride. Several studies suggest that finasteride has activity against prostate cancer and may be beneficial in prolonging the interval time between IAD cycles.[32,33] Tucker et al evaluated TAB in 77 men treated for a median of 13 months and continuing finasteride as maintenance therapy.[34] Combination therapy reportedly resulted in shorter time to undetectable PSA; however, it appears to be less useful in men with high risk features, such as Gleason 8-10 disease and those with PSA> 20 ng/ml. Other retrospective studies demonstrate that the addition of finasteride reduces PSA velocity,[35] lengthens time off intervals,[35,36] and increases quality of life.[36] Compared to standard IAD, no change has been found in progression to androgen-independent CaP.[36] A limitation of these studies is that IAD was examined as primary therapy in most patients.

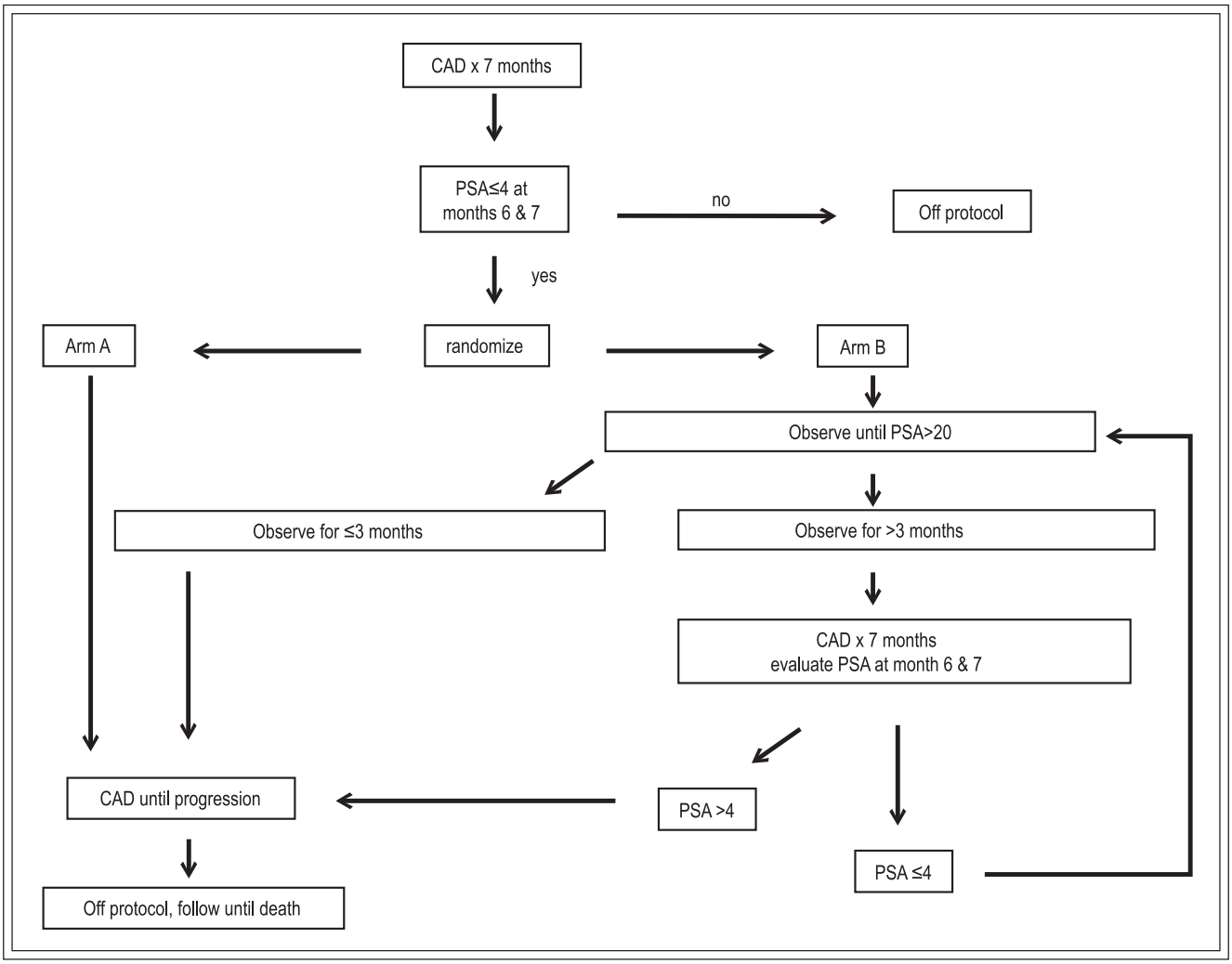

Figure 3. SWOG 93-46 randomization and treatment protocol outline. Patients in arm A receive continuous androgen deprivation, whereas patients in arm B initially receive intermittent androgen deprivation.

Conclusions

The usefulness of ADT in combination therapy is dependent on the type of primary treatment provided and the degree of disease. Though negative surgical margins may be more achievable with NADT prior to radical prostatectomy, the lack of a survival benefit does not support its clinical use for locally advanced cases. On the other hand, the addition of NADT to radiotherapy may improve disease outcome, particularly for patients with low-grade, bulky disease.

Adjuvant ADT to both radical prostatectomy and radiotherapy is an important complement to effective treatment in locally advanced cases. ADT may increase survival and decrease recurrence in patients with positive lymph nodes at surgery. As an adjunct to radiotherapy, only long-term ADT improves survival in high-risk patients, while short-term administration may be suitable for those at intermediate risk. Until prospective studies are conducted, there is no data to support a survival benefit for neoadjuvant or adjuvant ADT in patients undergoing brachytherapy or cryotherapy. However, reduction in tumor volume may be necessary for effective treatment of bulky disease. Men unsuitable for local therapy may also derive benefit from ADT in terms of enhanced quality of life and prolonged survival if they are at high risk of CaP-specific death.

Alternative strategies, such as IAD, TAB, and combination therapy with chemotherapy, remain to be established in the clinical setting. Thus far, IAD has not been proven to delay progression to androgen independence or lengthen survival time; however, improved quality of life makes it a more appealing

approach to hormonal therapy. Long-term data from prospective, randomized trials will help validate the use of IAD.

Beyond palliative care, ADT has clinical significance for many men with both local and metastatic prostate cancer, yet careful patient selection is necessary to ensure appropriate application. Future trials stratifying outcomes by risk groups will help to clarify which patients benefit most from hormonal therapy as well as determine the best strategy for administration.

Disclosure

Dr. Christopher Evans is a member of the Speakers' Bureau for Boehringer Ingelheim. He is on the advisory board for Boehringer Ingelheim and AstraZeneca and an investigator for Astra Zeneca. Dr. Thomas Keane is a member of the Speakers' Bureau for AstraZeneca, Cytogen Corporation, Auxilium Pharmaceuticals and Sanofi-Aventis. He is on the advisory board for Sanofi-Aventis and has done research for Cytogen Corporation. □

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