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REVIEW

Radiotherapy combined with hormonal therapy in prostate cancer: the state of the art

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Abstract: Androgen-deprivation therapy (ADT) is used routinely in combination with definitive external beam radiation therapy (EBRT) in patients with high-risk clinically localized or locally advanced disease. The combined treatment (ADT–EBRT) also seems to play a significant role in improving treatment results in the intermediate-risk group of prostate cancer patients. On the other hand, there is a growing body of evidence that treatment with ADT can be associated with serious and lifelong adverse events including osteoporosis, cardiovascular disease, diabetes, and many others. Almost all ADT adverse events are time dependant and tend to increase in severity with prolongation of hormonal manipulation. Therefore, it is crucial to clearly state the optimal schedule for ADT in combination with EBRT, that maintaining the positive effect on treatment efficacy would keep the adverse events risk at reasonable level. To achieve this goal, treatment schedule may have to be highly individualized on the basis of the patient-specific potential vulnerability to adverse events. In this study, the concise and evidence-based review of current literature concerning the general rationales for combining radiotherapy and hormonal therapy, its mechanism, treatment results, and toxicity profile is presented.
Keywords: prostate cancer, radiotherapy, androgen deprivation, combined treatment

Overview

Over the past 2 decades, prostate cancer (PC) patients have become the largest cancer population among all cancer patients in the United States and European Union countries. PC is the second and the third leading cause of cancer deaths in males in the United States and European Union countries, respectively.[1] The most common form of treatment for advanced PC is androgen-deprivation therapy (ADT), which can take the form of either surgical castration (orchiectomy) or medical castration (with luteinizing hormone-releasing hormone [LHRH] agonist).[2] In addition, more and more patients with unfavorable intermediate- and high-risk adenocarcinoma of the prostate are treated with combination of ADT and primary external beam radiation therapy (EBRT), which seems to be the most appropriate treatment.[3–5] As shown in a Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) report, the use of neoadjuvant hormones with radiotherapy (RT) increased from 9.8% to 74.6% during 1989–1992 and 1999–2001, and from 15.3% to 89.5% during the same periods in high-risk patients.[6] A report by Shahinian et al indicated that use of ADT increased steadily throughout the 1990s among men of all ages with PC who had all stages and grades of tumor.[7] These numbers highlight the need for good understanding of such treatment approach. On the other side, as the role of ADT in the treatment algorithm of PC continues to evolve, there has been increasing attention toward identifying and

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preventing ADT-associated adverse events in recent literature. Common side effects associated with ADT include skeletal complications, metabolic and cardiovascular complications, sexual dysfunction, hot flashes, periodontal disease, cognition, and mood disorders.[8,9] Some of the abovementioned adverse events can be associated with serious and lifelong disability, morbidity, and possibly mortality. Almost all ADT adverse events are time dependant and tend to increase in severity with prolongation of hormonal manipulation. Therefore, it is crucial to clearly state the optimal schedule for ADT in combination with EBRT, that maintaining the positive effect on treatment efficacy would keep the adverse events risk at a reasonable level. To achieve this goal, treatment schedule may have to be highly individualized on the basis of the patient-specific potential vulnerability to adverse events. In this paper, the concise and evidence-based review of current literature concerning the general rationales for combining RT and hormonal therapy (HT), its mechanism, treatment results, and toxicity profile is presented.

Rationales for combined treatment ADT–EBRT

In an early work, Huggins and Hodges stated that male hormones promote the growth of both prostate gland and cancer cells.[10] However, recently it has been recognized that the relationship between serum levels of testosterone and PC progression is not that straightforward. Very low (castrate) concentrations of serum testosterone are enough to fulfill its activating role on the PC cell through the so-called aberrant androgen-signaling pathways.[11,12] Moreover, there is an evidence for a significant increase in local synthesis of testosterone within prostate stimulated by castrate levels of serum hormone.[13] Even so, the incomplete eradication of testosterone with surgical or pharmacological castration has proved to improve the results of RT, and multiple studies looked into the possible mechanism and character of that interaction.

The idea that ADT added to RT may improve the results of combined treatment is based on an earlier experience in the application of neoadjuvant HT with surgery.[14] Neoadjuvant surgical trials have shown response rates (reduction of prostate volume, down-staging, and reduction of positive margin) approaching 90% when hormonal treatment prior to surgery was administered. However, this modality only reduces the number of positive postoperative margins after radical prostatectomy (RP), but without any influence on overall patient survival.[15] The mechanism whereby HT and RT interact has been studied in vivo in animal models. In the original article by Zietman et al, the Shionogi in vivo tumor system has provided the basis for our understanding of the mechanism behind interplay between ADT and RT. The tumors, designed to mimic PC, were implanted into severe combined immune-deficient mice.[16] Then radiation combined with hormonal manipulation (orchiectomy) was performed at varying time sequences relative to each other. The results showed that ADT improved the tumor response to radiation, which was reflected by reduction in the RT dose needed to control 50% of tumors (TCD50). Moreover, it was observed that when orchiectomy was performed prior to RT, much lower doses of radiation were required to achieve the given level of tumor control than if performed after or during RT. The authors conclude that increased overall cell kill seems to be a mechanism responsible for the combined effects of ADT and RT. Therefore, the decrease in the number of clonogenic cancer cells due to androgen-ablation therapy should enhance the effects of RT in tumors at the same dose range.[17] In another in vivo study, RT and androgen-ablation sequencing were evaluated in the R33270G Dunning rat prostate tumor model.[18] It was found that the median post-treatment tumor doubling time was significantly longer in the group that received RT after neoadjuvant androgen ablation compared to all the other treatment groups, including the RT with concurrent or adjuvant androgen-deprived groups. The possible mechanism of ADT–EBRT interaction in that study was the diminished growth velocity of the surviving PC cells after neoadjuvant ADT.

Other more clinical observations shed some light on ADT–EBRT interactions. Generally, androgen deprivation combined with RT is thought to influence the results of treatment due to local and/or systemic actions. However, whether the increased efficacy of ADT–EBRT is the result of an improved local treatment (radiosensitizing effect) or systemic eradication of micrometastases or the combination of both remains an unanswered question. Obviously, ADT leads to shrinkage of the entire prostate gland volume. It has very practical implications for RT. First, the field dimensions used in RT can be smaller, thereby allowing administration of a higher total dose without increased side effects to healthy tissue.[19] Data from numerous studies indicate that neoadjuvant HT results in substantial tumor volume reduction, ranging from 30% to 40%.[20] Another postulated mechanism refers to possible enhanced oxygenation (and related increased loco-regional RT effectiveness) of the hypoxic PC cells by improving blood flow with decreasing interstitial pressure when the total amount of cancer cells in the tumor is diminished by ADT.[21] It is also plausible that apoptosis induced by HT could affect cancer cells in which apoptosis was not activated by RT.[22] The apoptotic mechanism could also be relevant for the systemic interaction of ADT–EBRT by prevention of the subsequent distant micro metastases. The other systemic interaction scenario includes an increase in tumoricidal immune system response, which has been postulated to be a low-androgen-dependent state.[23]

Efficacy of EBRT–ADT combinations

Low-risk PC patients

There is probably no role for ADT in men with low risk for biochemical recurrence PC (T1–T2a, Gleason score [GS] 6 or below, prostate-specific antigen [PSA] below 10). Nevertheless, large number of patients with localized PC are receiving ADT as primary or neoadjuvant treatment, yet the clinical evidence do not support the use of such treatment. As reported by Lu-Yao et al, the ADT as a primary treatment for low-risk PC does not improve survival.[24] Generally, for low-risk PC patients, no published mature data on combined EBRT–ADT treatment exist from prospective randomized clinical trials. However, the first results of Radiation Therapy Oncology Group (RTOG) 94-08 randomized trial, which completed accrual in 2001 and has been designed to ascertain whether men with stage T1b–T2 PC and a serum PSA of 20 ng/mL or less benefit from the addition of ADT given for 4 months before and concomitantly with EBRT, has been presented as late-breaking news on recent ASTRO 2009, in November 2009.[25] This landmark study, with 1,979 participants, is the largest PC study to date among studies evaluating ADT–EBRT and is still ongoing. Originally, the study was designed to evaluate the treatment of men with low-risk PC only, but the definition of low risk evolved as the study got underway. About one-third of the patients were at low risk (n = 685), which was defined as a GS of 6 or less with a PSA level of 10 ng/mL or less and a tumor stage of T2a or less. About one half of the patients were at intermediate risk (n = 1068), which was defined as a GS of 7, a GS of 6 or less and a PSA of 10–20 ng/mL, or a GS of 6 or less and stage T2b disease. The remaining patients were at high risk (n = 226), with GS of 8–10. Study participants were randomized to short-term ADT (2 months before and 2 months during radiation) plus radiation therapy, or radiation therapy alone. At 8 years, the overall and disease-specific survival rates in low-risk patients treated with hormones and radiation were comparable to those treated with radiation alone. Specifically, the overall survival (OS) rate at 8 years for patients treated with hormones and radiation was 76%, compared with 73% for those treated with radiation alone (hazard ratio [HR], 1.07; 95% confidence interval [CI]: 0.83–1.39). The disease-specific survival rate at 8 years for patients treated with hormones and radiation was 98%, compared with 99% for those treated with radiation alone (HR, 1.07; 95% CI: 0.83–1.39).

Practically, no data or conclusions for low-risk PC patients can be pooled out of previous EBRT–ADT trials because most of them consisted of patients with T2C or higher stage tumors. In a study conducted by Bolla et al T1-T2 patients were also included, though only if they were also of GS 7–10, which also refers to a higher risk group than that deemed low risk according to National Comprehensive Cancer Network classification.[26]

Besides the RTOG trial, the only available evidence for the use of combined treatment can be sought in retrospective studies. D'Amico and associates reported results of a large retrospective study (N = 1586) of men treated with 3D-CRT plus or minus ADT for low-risk, intermediate-risk, and high-risk PC.[27] In this study, the median radiation dose was 70.2 Gy, and ADT was used in 276 men for 2 months before radiation therapy, during treatment, and for 2 months after treatment was completed. With a median follow-up of 51 months, the 5-year PSA relapse-free survival for men with low-risk PC was 92% with the addition of ADT vs 84% without ADT ($P = 0.09$). The issue of RT–HT in low-risk PC patients was also indirectly addressed by a retrospective analysis conducted by Ciezki et al.[28] The study included 1,668 patients with low- and intermediate-risk PC treated at The Cleveland Clinic Foundation with EBRT, RP, or prostate brachytherapy with or without androgen deprivation during 1996–2001. The 5-year biochemical recurrence-free survival (BRFS) rate was 90% vs 93% for EBRT alone or with ADT in low-risk patients.

Intermediate-risk PC patients

None of the completed prospective randomized clinical trials in PC have directly addressed the usage of EBRT–ADT combination in the group of intermediate-risk patients. However, results of three large randomized trials in which intermediate-risk patients constituted a significant percentage have been published or announced during last few years.

Most recently, data from RTOG study 94-08, which sought to determine whether 8-week neoadjuvant ADT improves RT outcome for patients with clinical stage II PC with a low to intermediate relapse risk, were presented on ASTRO 51 in Chicago.[29] About 54% of the patients accrued for that trial were at intermediate risk (n = 1068), which was defined as a GS of 7, a GS of 6 or less and a PSA of 10–20 ng/mL, or a GS of 6 or less and stage T2b disease. In the study, total androgen suppression was achieved with flutamide 250 mg twice daily and either goserelin 3.6 mg once a month or leuprolide 7.5 mg once a month. The HT apparently benefited men with intermediate-risk disease. At 8 years, the overall and disease-specific survival rates were favorable in intermediate-risk patients treated with hormones and radiation, compared with those treated with radiation therapy alone. Specifically, the OS rate at 8 years for patients treated with hormones and radiation was 72%, compared with 66% for those treated with radiation alone (HR, 1.23; 95% CI: 1.02–1.49). The disease-specific survival rate at 8 years for patients treated with hormones and radiation was 98%, compared with 92% for those treated with radiation alone (HR, 2.44; 95% CI: 1.47–4.04).

The DFCI 95096 trial by D'Amico et al consisted of a limited course of androgen deprivation combined with radiation (N = 206) for clinically localized PC (GS > 7 or a serum PSA > 10 ng/mL or evidence of extraprostatic disease). Patients were randomized to receive radiation therapy to a dose of 70 Gy alone or 70 Gy radiation plus 6 months of ADT. Approximately 60% of patients were at intermediate risk. At a median follow-up of 4.52 years, men treated with the combination of radiation plus androgen deprivation had a significantly higher OS than men treated with radiation alone (actuarial 5-year survival is 88% vs 78%).[30] What is special about this trial is that all-cause mortality estimates were stratified by randomized treatment group and further stratified in a postrandomization analysis by the comorbidity score. In the latest update with a median follow-up of 7.6 (range, 0.5–11.0) years, 74 deaths have occurred. A significant increase in the risk of all-cause mortality (44 vs 30 deaths; HR, 1.8; 95% CI: 1.1–2.9; $P = 0.01$) was observed in men randomized to EBRT compared with EBRT–ADT. However, the increased risk in all-cause mortality appeared to apply only to men randomized to EBRT with no or minimal comorbidity (31 vs 11 deaths; HR, 4.2; 95% CI: 2.1–8.5; $P < 0.001$). Among men with moderate or severe comorbidity, those randomized to EBRT alone vs EBRT–ADT did not have an increased risk of all-cause mortality (13 vs 19 deaths; HR, 0.54; 95% CI: 0.27–1.10; $P = 0.08$). The authors concluded that the addition of 6 months of ADT to EBRT resulted in increased OS in men with localized but unfavorable-risk PC and that this result may pertain only to men without moderate or severe comorbidity.[31]

The third trial conducted was performed by The Trans-Tasman Radiation Oncology Group – TROG 96.01. There were 802 men accrued with locally advanced PC of which approximately 20% fell into definition of intermediate-risk PC.[32] The trial had three arms, patients were randomized to RT alone, 3 months of neoadjuvant hormones with RT, or 6 months of neoadjuvant hormones with RT. The protocol prescription was 66 Gy to the prostate and seminal vesicles, without whole pelvic RT. Five-year PSA disease-free survival was significantly improved in the both 3-month arm (52%; $P = 0.002$) and 6-month arm (56%; $P < 0.0001$) as compared to the control arm (38%). However, the 6-month arm (94%) showed significantly improved prostate-cancer-specific survival (PCSS; 0.56 [0.32–0.98]; $P = 0.04$) compared with no androgen deprivation, while for the 3-month arm, the PCSS (92%) was not significantly different from the control arm (91%). Interestingly, also 5-year distant failures were significantly less in the 6-month arm (13%) but not for the 3-month arm (22%) as compared to the control arm (19%).

Moreover, some data and conclusions about the efficacy of EBRT–ADT in this group of patients may be derived indirectly from the retrospective subset analyses of previously described randomized clinical trials because some intermediate-risk PC patients were included in RTOG 85-31, European Organisation for Research and Treatment of Cancer (EORTC) 22863, RTOG 86-10, and RTOG 92-02. In all of these trials, investigational arms with EBRT–ADT (or long-term EBRT–ADT vs short-term EBRT–ADT in the case of RTOG 92-02) showed benefit in efficacy end points such as local control (LC), progression-free survival (PFS), BRFS, and incidence of distant metastases. Moreover, the latest update of RTOG 85-31 at the 10-year follow-up showed benefit in OS for all patients in the EBRT–ADT arm. The subset analysis of RTOG 86-10 at 8 years showed improvement in OS for patients with bulky (T2C–T4) tumors but a GS of 2–6.

As for ongoing trials, the definitive results of trial RTOG 99-10, which already completed accrual for randomized Phase III to evaluate the duration of NCHT (8 weeks vs 28 weeks) with EBRT in intermediate-risk PC patients, are still awaited.[33] Also, the RTOG 08-15 study is underway to evaluate more modern high-dose radiation methods and HT in these intermediate-risk patients.[34]

High-risk PC patients

During the last decade, the results of several prospective randomized clinical trials have indicated that combined treatment (androgen ablation plus RT) leads to improved treatment results. One of these well-documented clinical trials was carried out by Pilepich et al.[35] In this trial (RTOG 8531), the influence of androgen depletion combined with RT on the results of treatment was evaluated. Patients were randomized to receive RT alone or RT plus adjuvant goserelin (LHRH agonist), which was introduced in the last week of RT and continued until the disease progressed or as long as it was tolerated by the patient. RT fields in the first phase of treatment encompassed pelvic lymph nodes, dosed from 44 to 50 Gy, followed by an additional dose of 20–25 Gy to the prostate. Eligible patients had pelvic lymph node involvement (N1) or T3-T4. In the mid 90s, PSA determination became mandatory for all patients participating in the trial. At the median follow-up time of 4.5 years (range; 0.2–9.8 years), 84% of patients on the combined therapy arm and 71% of those on the RT-alone arm had no evidence of local recurrence ($P < 0.0001$). The update of RTOG trial 85-31 presented in 1999, with a median follow-up time of 5.6 years for all patients and 6 years for patients who were alive, showed an improvement in cause specific survival in the group of patients receiving additional HT treatment ($P = 0.019$).[36] The latest update was presented in 2005: after 10 years, there was a 10% advantage in OS for the HT arm ($P = 0.002$).[37] Patients with GS of 7–10 showed the greatest improvement in survival rate. In the next study (RTOG 8610) carried out by Pilepich et al, patients received neoadjuvant (2 months prior to RT) then androgen ablation (goserelin + flutamide) during RT in the study group, and RT alone in the control group.[38] The RT technique was similar to that applied in trials RTOG 8307 and 8531. The results of this trial indicated that patients in the combined therapy group had better LC, with 5- and 8-year failure rates of 25% and 37%, respectively, compared with 36% and 49% in the RT-alone group ($P < 0.002$). The most recent analysis of RTOG 86-10 indicated that in patients with GS 7–10, the regimen has not resulted in a significant improvement in either loco-regional control or survival. However, in patients with GS 2–6 tumors, short-course HT administered before and during RT resulted in a highly significant improvement in OS (70% vs 52%, $P = 0.015$).[39] An interesting analysis combining the RTOG 85-31 and RTOG 86-10 trials was performed by Horwitz et al.[40] According to this study, the statistically significant benefit in bNED control ($P = 0.0002$), DMF ($P = 0.05$), and CSF ($P = 0.02$) in patients receiving long-term HT was limited to centrally reviewed GS 7 and 8–10 tumors.

The results of the next well-documented randomized trial conducted by the EORTC come from Europe. In this study, which was reported by Bolla et al, long-lasting adjuvant HT during follow-up was compared to follow-up without additional HT.[41] In the first phase of this trial, goserelin acetate (LHRH analogue) and cyproterone acetate (150 mg/d/1 mo) were administered prior to RT concurrently during RT in both arms of the study. Thereafter, only in the investigational arm, androgen depletion therapy (LHRH analogue) was continued for 3 years. Patients in both groups received a 50 Gy dose of radiation to the pelvic lymph nodes and then an additional 20 Gy dose to the prostate. The results of this study were particularly noteworthy because it compared short neoadjuvant androgen ablation treatment with long-term adjuvant therapy. This trial indicated that LC in the investigational arm (combined treatment) was 97% compared to 77% in the control arm (no further treatment after RT) at the 45-month follow-up. The 5-year OS in the combined treatment arm was 79% vs 62% in the RT-alone group, respectively.

Another important study, reported by Laverdiere et al compared the following three treatment methods: RT alone, neoadjuvant-combined androgen blockade (3 months) + RT, and neoadjuvant-combined androgen blockade (3 months) + RT + adjuvant-combined androgen blockade (10.5 months).[42] The results of this study showed the advantage of neoadjuvant and adjuvant HT over RT alone. The study found that patients treated with a 64 Gy dose in a combined fashion noted 28% positive biopsies compared to 65% treated with RT alone. However, the androgen deprivation given 3 months before and 6 months after the RT was associated with only a 5% rate of positive biopsies. Data concerning the influence of combined therapy on treatment outcome are also based on observation of 1,554 patients entered in trial RTOG 9202 conducted by Hanks et al.[43] According to the trial protocol, all the patients received goserelin and eulexin 2 months before and then during RT. After completion of RT, they were randomized without any further therapy or were administered additional goserelin alone for 24 months. The study showed that significant improvement in local progression rate (6.2% vs 13%), disease-free survival (54% vs 34%), freedom from distant metastases (11% vs 17%), and biochemical control (46% vs 21%) was achieved in the group of patients who were treated long-term hormonally. It should be emphasized that subset analyses (T3, T4, and T2 with GS 8–10) showed no significant OS difference (77% vs 80%) over 5 years.

One of the latest randomized clinical trials is the Early PC (EPC) program, the largest treatment trial of patients with localized or locally advanced PC. The program is helping to define which patients benefit, and which do not, from early or adjuvant anti-androgen therapy. Third analysis results, at 7.4-years median follow-up, were recently released. The program comprises three randomized, double-blind, placebo-controlled trials designed for combined analysis. Men (n = 8,113) with localized (T1-2, N0/Nx) or locally advanced (T3-4, any N; or any T, N+) PC (all M0) were recruited. Patients received bicalutamide 150 mg (n = 4,052) or placebo (n = 4,061) once daily plus standard care (RT, RP, or watchful waiting [WW]). The primary endpoints were OS and objective PFS. Bicalutamide significantly improved OS in patients with locally advanced disease who received RT (HR, 0.65; $P = 0.0276$); this was driven by a lower risk of death due to PC (16.1% vs 24.3%). The ongoing EPC program sheds light on the role of anti-androgen therapy and indicates significant clinical benefit from the addition of bicalutamide 150 mg to standard care for patients with locally advanced disease; in particular, an OS benefit was seen in men who received RT.[44]

During the last decades, there were a few papers published, which showed that long-term adjuvant ADT combined with RT for high-risk PC group is related with significant improvement in OS. On the other hand, because long-term ADT caused several side effects, Bolla et al have conducted a randomized clinical trial (EORTC 22961, the so-called Bolla's second trial) in which investigators compared the effects of a shorter treatment regimen (6 months of ADT) to long-term regimen (36 months of ADT).[45] In this non-inferiority trial, 1,113 patients were included, but 970 patients underwent randomization. Criteria for participation in this trial included T1c to T2a–b, pN1 or pN2, M0 or with T2c to T4, cN0 to cN2, and M0, baseline level of PSA up to 40 times the upper limit of the normal range, and a World Health Organization performance status of 0–2. The first 6 months of androgen suppression consisted of complete androgen blockade (CAB) with an LHRH analogue, initiated on the first day of irradiation, and an antiandrogen agent (750 mg of flutamide per day or 50 mg of bicalutamide per day), initiated 1 week before the start of treatment with the LHRH analogue. The patients assigned to long-term suppression continued to be treated with the same LHRH analogue but without the antiandrogen for another 2.5 years. RT was applied in the first phase to the whole pelvis (50 Gy) and then to the prostate gland up to 70 Gy in both arms. Investigators indicated that after 6.4 years of follow-up, a 5 years, overall mortality was higher with short-term ADT than with long-term ADT, as well PC-specific mortality increased by 3.8% and 1.5%, respectively. So, in conclusion of this trial, authors stated that a long-term ADT combined with RT should be the gold standard for high-risk PC patients.

ADT toxicity

Sexual dysfunction

The typical and first described adverse effects of ADT are impotence and loss of libido. The relationship between androgen ablation and sexual function has been studied in several series.[46] In one series, Potosky et al compared men selecting WW (n = 416) with men selecting ADT (n = 245) during the first year following cancer of the prostate (CaP) diagnosis.[47] Patients completed sexual and quality of life surveys at baseline, 6 months postdiagnosis, and 12 months postdiagnosis. Among men reporting some sexual interest at baseline, 54% of the ADT group vs 13% of the WW group reported no interest in sexual activity at approximately 12 months postdiagnosis ($P < 0.001$). Among men who were potent at baseline, 80% of the ADT group compared to 60% of the WW reported impotence at 1-year follow-up ($P < 0.001$). Fowler et al compared health-related quality of life (HRQOL) outcomes in androgen-deprived (n = 298) and nonandrogen-deprived men (n = 1,095) following RP in a survey-based study using Medicare Provider and Analysis and Review files. Overall, 166 men in the ADT group and 886 men in the non-ADT group responded to the survey questions regarding erectile dysfunction. Patient receiving ADT reported higher rates of postprostatectomy impotence (72% vs 55%), but similar rates of impotence over the month prior to the survey (23% vs 22%). Regarding the quality of erections, 3% (vs 11%) of androgen-deprived men reported erections insufficient for intercourse, and only 2% (vs 12%; $P < 0.0001$) reported erections firm enough for intercourse. With regard to libido, 69% (of the 170 responders) in the ADT group reported no sexual drive over the 30 days prior to the survey compared to 29% (of the 888 responders) in the non-ADT group ($P < 0.0001$).[48]

Quality of life

Currently, no Level I evidence exists that clearly demonstrates association of ADT with a decreased HRQOL, and no consensus recommendations are published to minimize HRQOL-related adverse effects. Several series have documented an association between ADT and declining HRQOL.[49] For example. Dacal et al compared HRQOL between men undergoing short-term ADT (<6 months), long-term ADT (>6 months), and healthy controls. When using the MOS questionnaire, they found that men receiving any duration of ADT demonstrated significantly worsened HRQOL. In particular, ADT recipients demonstrated decreased scores in physical component health summary ($P < 0.001$), physical function domain ($P < 0.001$), and general health category ($P < 0.001$).

Notably, a time-dependent relationship between decreased HRQOL and duration of ADT was not established.[50] These findings have been supported by other studies demonstrating the negative impact of ADT on cognition, sexual function, social interaction, role functioning, and an increase in the level of emotional distress.[51] In addition to effects on overall HRQOL, recent data investigating the association between ADT and psychiatric illness has documented an almost twofold increase in the risk of de novo psychiatric illness following ADT induction.

Vasomotor symptoms "hot flashes"

The so-called "hot flashes" or, more precisely, vasomotor flushings are a common and well-described treatment toxicity in men undergoing androgen ablation and are one of the most frequently reported adverse consequences of ADT. Spetz et al performed a prospective analysis comparing the incidence of hot flashes in men receiving CAB to that in men receiving estrogen therapy for treatment of PC.[52] In this study, in 915 patients with metastatic disease, 458 were treated with polyestradiol phosphate and 457 patients received CAB. Of men receiving CAB, 74.3% reported hot flashes compared to 30.1% in men receiving estrogen therapy ($P < 0.001$). Further, a significantly greater percentage of men treated with CAB were "greatly distressed" by the hot flashes (11.3% vs 2.6%, $P < 0.01$) and reported at least 4 hot flashes per day (33.7% vs 2.7%, $P < 0.001$). ADT-associated vasomotor flushing remains a common complaint reported by men receiving this therapy and is reported in up to 80% of men receiving ADT. Interestingly, megestrol acetate has been demonstrated to reduce hot flash symptoms by up to 85%. On the other hand, chills, weight gain, and carpal tunnel-like pain are the reported side effects of megestrol acetate.[53]

Endocrine dysfunction and metabolic syndrome

Male hypogonadism is recognized as an independent risk factor for the development of endocrine dysfunction.[54,55] In particular, there is increasing evidence supporting an association between ADT and increased risk of the metabolic syndrome and its associated adverse endocrine and end-organ effects.[56] Metabolic syndrome is diagnosed when three of five criteria proposed by the Adult Treatment Panel III are met, including fasting plasma glucose >100 mg/dL, serum triglyceride level >150 mg/dL, serum high-density lipoprotein (HDL) < 40 mg/dL, waist circumference >102 cm, and blood pressure >130/85. In one study, a significantly higher overall prevalence of abdominal obesity ($P = 0.007$), hyperglycemia ($P = 0.007$), and hypertriglyceridemia ($P = 0.06$) in ADT group was noted – all factors that contribute to the diagnosis of metabolic syndrome. Further, the prevalence of the metabolic syndrome was found to be significantly higher in the men receiving ADT (55%) compared to both the non-ADT group (22%) and eugonadal controls (20%, $P = 0.03$). The insulin resistance is a major factor of the metabolic syndrome and has also been associated with ADT.[57] In the study by Smith et al, 25 men with locally advanced or recurrent CaP and no evidence of metastasis or diabetes were studied for ADT-related effects on insulin resistance. Patients received a 12-week course of CAB (leuprolide depot and bicalutamide) and baseline, and follow-up comparisons were made between the following parameters: plasma glucose, plasma insulin, hemoglobin A1c, lipid profiles, and percentage of body fat. Mean percent body fat mass increased 4.3% ± 1.3% ($P = 0.002$) after 3 months, while percent lean body mass decreased 1.4% ± 0.5% ($P = 0.006$). Further, ADT demonstrated significant effects on all of the lipid indices assessed, with rises in total cholesterol (9.4% ± 2.4%, $P < 0.001$), HDL cholesterol (9.9% ± 2.9%, $P = 0.01$), low-density lipoprotein cholesterol (8.7% ± 4.7%, $P = 0.09$), and triglycerides (23% ± 8.0%, $P = 0.04$). No changes in fasting blood glucose were seen during the study; however, significant rises were seen in plasma insulin levels ($P = 0.04$) and mean serum HbA1c levels ($P < 0.001$). Further, insulin sensitivity significantly decreased by nearly 13% ($P = 0.02$), and one patient was diagnosed with diabetes mellitus (DM) at the completion of the study.[58] In another series of 73,196 men with local and regional CaP from the Surveillance, Epidemiology, and End Results (SEER) database, a significant increase in the incidence of DM was noticed in men receiving ADT ($P < 0.001$) when compared to those not receiving ADT. Further, the duration of ADT was identified as a predictor for increased risk of subsequent diabetes, even in patients receiving only short courses of ADT.

Osteoporosis and skeletal fractures

Osteoporosis in men has gained significant clinical attention over the last decade. T-score criteria for the diagnosis of osteoporosis and osteopenia are still evolving; however, it is estimated that using fractures as a clear endpoint for the disease, males have a 13%–25% lifetime risk of developing osteoporosis. Hypogonadism is well described as one of the major causes of osteoporosis in men along with alcohol abuse, glucocorticoid excess, low-dietary calcium, vitamin D deficiency, and sedentary lifestyle. The increasing use of ADT in current practice patterns for the treatment of local and advanced CaP has made ADT one of the leading causes of hypogonadism and thus osteoporosis in men.[59,60] In a contemporary series of 395 men receiving ADT, Malcolm et al identified ADT as an independent risk factor for the development of osteoporosis and nonpathologic fractures. In this series, 23% of men receiving ADT developed osteoporosis, while 7% were diagnosed with nonpathologic fractures. Further, duration of ADT was identified to be an independent predictor for the development of osteoporosis ($P < 0.001$) and was on average 49% longer in patients diagnosed with fractures ($P < 0.001$). Importantly, the development of osteoporosis was positively associated with the development of nonpathologic fractures in this cohort ($P < 0.001$). Another study brought evidence that gonadotropin-releasing hormone (GnRH) agonists increase the risk of fractures in men receiving ADT when compared to controls.[61] Shahinian et al analyzed men with CaP from the SEER database to assess osteoporosis and fracture risk in the ADT population.[62] For men surviving at least 5 years from CaP diagnosis, the incidence of fractures was 19.4% for patients treated with GnRH agonists vs 12.6% for men treated with other modalities ($P < 0.001$). Further, Cox proportional-hazards regression analyses identified a statistically significant relationship between the number of GnRH injections in the first year following diagnosis and the risk for developing fractures, after adjusting for other clinicopathologic variables. Smith et al assessed the risk for fracture development in men with nonmetastatic disease who were treated with ADT.[63] Nearly 4,000 men with a history of ADT receipt were matched to men receiving no form of castration therapy (n = 7,774). Their comparison study demonstrated a significantly higher clinical fracture risk in the GnRH agonist group (7.88/100 vs 6.51/100 person-years at risk, $P < 0.001$). Further, ADT independently predicted future fracture risk in multivariate analyses, and longer treatment duration conferred a greater risk for subsequent fractures. The increased fracture rates in patients receiving HT are multifactorial, including higher incidence of metastatic bony lesions, fragility from disease and disease-related treatment, and decreased bone mineral density associated with ADT.[64]

Cardiovascular disease

Several retrospective studies suggested increased risk for cardiovascular disease in patients receiving ADT. In a study by Malcolm et al, 395 men receiving ADT were reviewed for incidence of cerebrovascular accident or myocardial infarction. Logistic regression demonstrated a time-dependent relationship between risk of myocardial infarction (HR, 2.12; $P = 0.03$) and cerebrovascular accident (odds ratio = 3.22, $P = 0.001$) and increasing duration of ADT administration.[65] Further in another study, Keating et al identified a higher incidence of coronary heart disease (HR = 1.16, $P < 0.001$), myocardial infarction (HR = 1.11, $P = 0.03$), and sudden cardiac death (HR = 1.16, $P = 0.004$) in men receiving ADT when compared to a control group. Additionally, the increased risk of coronary heart disease remained significantly increased even in men receiving ADT for as few as 1–4 months (HR = 1.29, $P < 0.001$). Myocardial infarction and sudden cardiac death also occurred at higher frequencies in the ADT group when stratified by duration of therapy, though this did not demonstrate statistical significance. Tsai et al directly examined the relationship between ADT and cardiac-related death in an analysis of the CaPSURE database.[66] Of 4,892 patients with organ-confined CaP, 1,015 received either neoadjuvant or adjuvant ADT, with median therapy duration of 4.1 months, in conjunction with local surgical or radiation treatment. Competing regression analyses that controlled for age, ADT administration, and a history of heart disease or diabetes mellitus at baseline were used to compare cardiac-related mortality rates between men receiving ADT or treated without castration. The authors found that in men treated with RP (n = 3,262), age (HR = 1.07, $P = 0.003$) and ADT use (HR = 2.6, $P = 0.002$) were significantly associated with an increased risk of cardiac-related death. Moreover, 5-year cumulative incidence estimates of cardiac death were higher in men receiving ADT when stratified by age ($P = 0.02$ for < 65 years, $P = 0.01$ for > 65 years). On the other hand, results of a recently completed EORTC randomized trial (Protocol 22961) comparing RT plus a total of 6 months of ADT to RT plus a total of 3 years of ADT in patients with locally advanced PC detected no significant difference in the incidence of fatal cardiac events at 5-year follow-up (4.0% vs 3.0%, respectively). Moreover, the recent systematic review performed by panel of specialist recommended that at present, based on the available evidence, it can only be stated that ADT may be related with cardiovascular disease risk.[67]

Remarks and conclusions

In the high-risk group of patients, combined treatment (RT–HT) produced therapeutic gain. For intermediate-risk patients, we have the first results of clinical trials RTOG 94-08, suggesting a statistically significant benefit. More precise conclusion can be made after the results of RTOG 99-10 trial. For low-risk PC patients, combined EBRT–ADT has no role in contemporary treatment guidelines. On the basis of the data reviewed from the literature, it can be concluded as follows:

1. ADT is easy to administer and requires no special technology. Neoadjuvant, concurrent, and long-term adjuvant androgen deprivation is standard treatment in conjunction with radiation therapy in the group of patients with high risk of failure (T3, PSA $>$ 20 ng/mL, GS $>$ 7). Neoadjuvant, concurrent ADT, and short-term adjuvant should be individually decided in intermediate-risk patients.
2. The optimal timing for application of androgen depletion has not yet been precisely determined. According to the current state of knowledge, approximately 2–3 months for neoadjuvant therapy is probably the optimal strategy. The best mode of neoadjuvant HT is represented by chemical castration combined with short antiandrogen treatment in the initial phase. Neoadjuvant HT should always be followed by ADT concurrent with RT. Adjuvant HT is recommended for high-risk patients for at least 2 years, but longer treatment could be beneficial, provided the toxicity of ADT is not of concern because of patient comorbidities. Studies have shown a survival benefit for patients with more advanced disease when longer adjuvant androgen suppression treatment was applied (3 years).

Disclosure

The authors report no conflicts of interest in this work.

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