Preoperative Androgen Deprivation Therapy for Localized Prostate Cancer: Delayed Biochemical Recurrence in High-Risk Disease

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Abstract

Androgen deprivation therapy (ADT) before surgery for prostate cancer is controversial. In a large, retrospective series with matched control subjects, we suggest that patients with high-risk localized prostate cancer might derive benefit from this approach.

Background: The role of preoperative ADT for localized prostate cancer is controversial; prospective assessments have yielded varying results. We sought to define a subset of patients with a higher likelihood of benefit from preoperative ADT. **Patients and Methods:** An institutional database including consecutive patients receiving definitive surgery for localized prostate cancer was interrogated. Patients recorded as having received preoperative ADT were matched in a 1:2 fashion to patients who had not received previous ADT. Patients were matched on the basis of clinicopathologic characteristics, use of adjuvant treatment strategies, and duration of prostate-specific antigen follow-up. Time to biochemical recurrence (TTBR) was compared using the Kaplan-Meier method and log-rank test for the overall study population and in subsets defined according to D'Amico risk. **Results:** No significant differences in clinicopathologic characteristics were noted between recipients (n = 101) and matched nonrecipients (n = 196) of preoperative ADT. Although not statistically significant, positive surgical margin rates, seminal vesicle invasion, and extracapsular extension were less frequent in patients receiving preoperative ADT. Furthermore, a lesser incidence of perioperative complications was noted in this group (7.4% vs. 18.4%). No significant differences were noted in TTBR between recipients and nonrecipients of preoperative ADT in the overall study population. However, among patients with high-risk disease, TTBR was significantly longer in patients who had received preoperative ADT ($P = .004$). **Conclusion:** The data presented herein suggest a potential benefit of preoperative ADT in patients with high-risk localized prostate cancer. Consideration should be given to enriching for this subset in preoperative studies of novel endocrine therapies.

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Introduction

Current guidelines for localized prostate cancer facilitate the selection of appropriate patients for either definitive radiation therapy or definitive surgical intervention when treatment is indicated.[1,2] Embedded within these guidelines are selected indications for use of androgen deprivation therapy (ADT) in association with these modalities. Based on prospective, randomized trials, patients with intermediate- or high-risk disease who choose to receive definitive radiation therapy should be offered neoadjuvant, adjuvant, or concomitant ADT of varying duration (4-6 months for intermediate-risk disease vs. 2-3 years for high-risk disease).[3,4] In contrast, the use of ADT as a preoperative adjunct to definitive surgery is not satisfactorily supported by existing evidence and is therefore absent from the guidelines.

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There appears to be renewed interest in exploring the role of ADT in the context of patients receiving radical prostatectomy. In the Southwest Oncology Group (SWOG) 9921 trial, patients with high-risk disease (defined as extraprostatic extension or high Gleason grade) were randomized to receive either ADT alone or ADT with mitoxantrone. Dorff et al reported outcomes for 481 patients receiving ADT in an adjuvant fashion in this study. In this group, biochemical recurrence-free survival was 92.5% at 5 years.[5] These values compare favorably with historical standards. Preoperative ADT has also been explored across multiple prospective and retrospective studies.[6] However, a cumulative interpretation of this literature is challenged by: (1) varying types of ADT used; (2) varying durations of ADT; and (3) disparate risk stratification schema used to classify patients receiving ADT.

Despite the controversy surrounding it, preoperative therapy for prostate cancer remains of substantial interest. Several preoperative trials that have either been reported or are ongoing assess newly approved therapies for metastatic castration-resistant prostate cancer, such as abiraterone or enzalutamide.[7,8] As similar studies emerge, it would be ideal to identify the subset of patients most appropriate for preoperative therapy. In the current study, we used a large institutional database to achieve these aims.

Patients and Methods

Patient Selection

Patients who had received ADT before prostatectomy were identified from the City of Hope Prostate Cancer Database. This database was established through an institutional review board-approved protocol that prospectively captures clinicopathologic data, treatment-related data, and a range of outcomes (surgical complications, time to biochemical recurrence [TTBR], survival, etc) among patients treated with robot-assisted radical prostatectomy. The database was established in 2000 and, since 2003, more than 5000 robotically assisted cases have been entered. The ADT patient population was selected from among the robotic cases, excluding patients who underwent salvage prostatectomy and those who received neoadjuvant chemotherapy or other preoperative therapy. Notably, ADT was comprised of luteinizing hormone-releasing hormone (LHRH) agonist therapy (excluding patients receiving LHRH antagonists) with or without antiandrogen therapy. Durations of therapy referred to herein are specific to the LHRH agonist, not antiandrogen. Notably, no patients in the currently examined cohort received preoperative therapy with novel endocrine agents, such as enzalutamide or abiraterone.

Matching Methodology

Patients who had received preoperative ADT were matched in a 1:2 fashion with patients who had received no preoperative ADT, using a computerized matching algorithm, GMATCH.[9] The following criteria were used to optimize matching (in order of priority): (1) clinical T-stage ($\leq$ T1c vs. $>$ T1c); (2) prostate-specific antigen (PSA) (0-10 vs. 10-20 vs. $>$ 20); (3) biopsy Gleason score ($\leq$ 6 vs. 7 vs. $>$ 7); (4) use of adjuvant radiotherapy (yes vs. no); (5) use of adjuvant hormonal therapy (yes vs. no); and (6) duration of PSA follow-up ($<$ 3 years vs. 3-5 years vs. $>$ 5 years).

Statistical Analysis

The clinicopathologic characteristics of recipients of neoadjuvant ADT and their matched counterparts were compared using the χ^2 or Fisher exact test (for categorical variables) or the Student t test or the Wilcoxon rank-sum test (for continuous variables), as appropriate. In addition, complications (either perioperative or during a 30-day postoperative period) were compared between the 2 groups in a similar fashion. Rates of adjuvant therapy use (radiation and androgen deprivation) were also compared. TTBR was characterized as the time from prostatectomy to the first time at which a PSA of $>$ 0.2 ng/mL was recorded. Using the Kaplan-Meier method with the log-rank test, TTBR was compared in recipients and nonrecipients of neoadjuvant therapy. The same comparison was then made within subgroups divided by risk (eg, low, intermediate, and high). Risk designations were in accordance with D'Amico criteria. Specifically, low risk features included cT1 to T2a disease, Gleason score $\leq$ 6, and PSA $<$ 10 ng/mL. Intermediate risk features included cT2b disease, Gleason score of 7, or a PSA of 10 to 20 ng/mL. High risk features included cT2c to T3 disease, Gleason score 8 to 10, or PSA $>$ 20 ng/mL.

Results

Patient Characteristics

As noted in Table 1, clinicopathologic characteristics of patients treated with preoperative ADT (n = 101) and matched patients without preoperative therapy (n = 196) were similar. Notably, 3 patients who had received preoperative ADT could not be matched by the criteria noted in the Statistical Analysis section, but were nonetheless included in the subsequently described results. The median age of the overall cohort was 66 years, most patients were Caucasian (81%), and based on the Charlson Comorbidity Index (CCI), there was little difference in the extent of comorbidity between the recipients and nonrecipients of preoperative therapy (median age-adjusted CCI, 5.0 in both groups). No significant differences in Gleason score, clinical T-stage, or baseline PSA were noted between groups, and the proportions of patients characterized as low-, intermediate-, or high-risk based on D'Amico criteria were similar.

Only a minority of patients (36%) received more than 3 months of preoperative ADT in the preoperative therapy group. A comparison of pathologic findings is delineated in Table 2. Patients receiving preoperative therapy had a fewer number of lymph nodes retrieved compared with patients with no preoperative therapy (3 vs. 4; $P = .001$); however, there was no significant difference in the positive lymph node rate between groups (3% for both). Differences in surgical Gleason score were also observed, although it has been advocated that Gleason scores not be provided for patients who receive preoperative therapy (hence a greater extent of missing data in this group). Positive surgical margin rates, seminal vesicle invasion, and extracapsular extension were all less frequent in patients receiving preoperative ADT, although these differences were not statistically significant.

Adjuvant strategies were used in only a small proportion of patients, and the extent of use was similar between arms. Approximately 12% of patients received adjuvant radiotherapy, and 15% of patients received adjuvant ADT. Use of adjuvant chemotherapy was minimal.

Operative Morbidity

Operative time was less in patients receiving preoperative ADT (2.9 hours vs. 3.0 hours; $P = .03$), although the numerical