Timing of Androgen Deprivation Therapy and its Impact on Survival After Radical Prostatectomy: A Matched Cohort Study

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Purpose: We assessed the impact of the timing of androgen deprivation on disease progression after radical prostatectomy for patients with localized prostate cancer.

Materials and Methods: We evaluated all patients who underwent radical prostatectomy between 1990 and 1999. Patients with pathological lymph node negative disease who received androgen deprivation therapy were then separated into 5 groups for analysis based on the time of hormone therapy initiation: 1—adjuvant androgen deprivation, 2—androgen deprivation therapy started at a postoperative prostate specific antigen of 0.4 ng/ml or greater, 3—at prostate specific antigen 1.0 or greater, 4—at prostate specific antigen 2.0 or greater and 5—at systemic progression. The first 4 groups were matched by clinical and pathological features to control groups who did not receive androgen deprivation after surgery using a nested, matched cohort design. Median followup for the entire cohort was 10 years. Clinical end points included systemic progression-free survival and cancer specific survival.

Results: After matching clinicopathological variables adjuvant androgen deprivation therapy was associated with improved 10-year systemic progression-free survival (95% vs 90%, $p < 0.001$) and 10-year cancer specific survival (98% vs 95%, $p = 0.009$), although overall survival for these patients remained unchanged (84% vs 83%, $p = 0.427$). In contrast, we found that men who started hormonal therapy at a postoperative prostate specific antigen of 0.4 or greater, 1.0 or 2.0 did not have improved systemic progression-free or cancer specific survival.

Conclusions: Adjuvant hormonal therapy modestly improves cancer specific survival and systemic progression-free survival after prostatectomy. The benefit of hormone therapy is lost when androgen deprivation is delivered at the time of prostate specific antigen recurrence or systemic progression.

Key Words: hormones, prostatic neoplasms, prostatectomy, survival

Radical prostatectomy is an established form of curative therapy for prostate cancer. Unfortunately even of patients with clinically localized disease between 15% and 25% will experience PSA recurrence after surgery, and 5% to 10% will die of prostate cancer.[1,2] Androgen deprivation therapy has long been accepted as an effective treatment for patients with advanced prostate cancer,[3] and adjuvant hormone therapy has been shown to improve survival for those undergoing radiation therapy[4–6] as well as for patients treated with RP for lymph node positive disease.[7] However, the optimal time to initiate hormonal therapy after surgery for patients with high risk, clinically localized disease remains in debate.[8] While some advocate withholding ADT until the development of symptomatic or radiographic metastases, others recommend immediate postoperative treatment. Alternatively many urologists initiate hormone therapy after biochemical recurrence is documented but before clinically evident systemic progression.

Thus, the goal of our study was to assess the impact of ADT timing on the risk of systemic progression and cancer specific death in a large cohort of patients treated with RP with long-term followup using a nested case-control design. We also identified clinical and pathological features that predict a favorable response to ADT after RP.

MATERIALS AND METHODS

Study Cohort

With approval from the Mayo Clinic institutional review board 8,290 patients who underwent RP for prostate cancer between 1990 and 1999 were identified from the Mayo Clinic Prostatectomy Registry. The clinicopathological and followup information in this registry is collected prospectively and updated annually. A minority of patients receive followup elsewhere and have their records updated by correspondence, leaving only 4% of participants for whom followup is incomplete. After exclusion of patients who received neoadjuvant therapy before surgery (743), refused research authorization (74), received adjuvant radiation treatment (378) and who were found to have lymph node metastases at

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RP (370), a total of 6,401 men remained and formed the current study cohort. This cohort was then divided into 5 groups for subsequent analysis: 1—patients who underwent adjuvant ADT within 90 days of surgery (580), 2—patients who initiated ADT at a PSA of 0.4 ng/ml or greater after RP (89), 3—patients who received ADT starting when PSA reached 1.0 ng/ml or greater after RP (99), 4—patients who started ADT at a PSA of 2.0 ng/ml or greater following surgery (77) and 5—patients not treated with ADT until systemic progression (78). Using a matched cohort design each of the first 4 groups was matched for clinical and pathological features to a corresponding control arm of patients who did not undergo ADT in the specified time frame. These features included age at surgery, clinical and pathological stage, clinical and pathological Gleason score, margin status, seminal vesicle involvement, tumor ploidy, and PSADT in patients studied at PSA recurrence. To enhance the statistical power of the study the control arms were matched to the study arms in a 2:1 ratio. Due to small patient numbers a matched analysis was not performed for group 5 because nearly all patients with systemic progression received ADT. Instead a multivariate analysis was performed to assess the effect of ADT on CSS in patients started on hormone therapy at the time of systemic progression.

RP and pelvic lymphadenectomy were performed by many surgeons using standard operative techniques. Pathological evaluation was done using a limited sampling technique on frozen tissue sections at surgery with subsequent examination of paraffin embedded sections the following day.[9,10] Tumor stage and grade were assigned using the 1997 Union International Contre le Cancer-American Joint Committee on Cancer TNM system and the Gleason system, respectively.[11,12] Tumor DNA ploidy was assessed by flow cytometry. ADT included luteinizing hormone-releasing hormone agonists, oral antiandrogens and orchiectomy. Medical hormone deprivation therapy was generally intended to be lifelong. However, given the retrospective nature of this study it is uncertain whether some patients discontinued hormonal therapy after a time.

Clinical End Points and Definitions

Postoperative followup was performed quarterly to semiannually for the first 2 years and annually thereafter by clinical assessment, measurement of serum PSA and other investigations as indicated. Using logarithmic regression analysis,[13] postoperative PSADT was calculated starting with the first detectable PSA after surgery and using all available PSA measurements in men who had at least 2 PSA measurements available that were separated by at least 90 days. Biochemical failure was defined as PSA 0.4 ng/ml or greater after RP.[14] Systemic progression was defined as demonstrable metastatic disease on imaging (radionuclide bone scintigraphy or plain film), or pathological evidence of prostate cancer in any postoperative tissue biopsy outside the prostatic fossa. For patients who died during the course

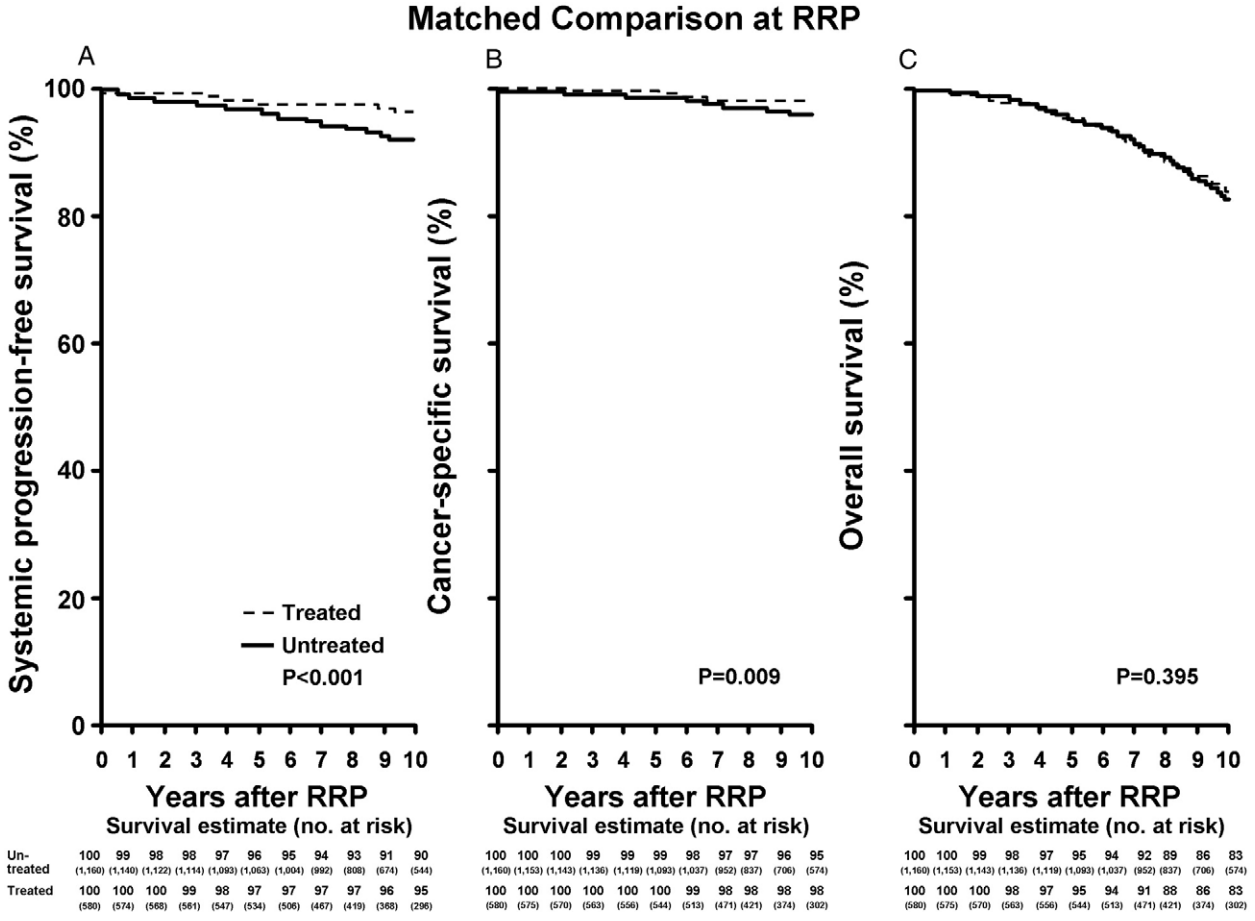

FIG. 1. Systemic progression-free survival (*A*), cancer specific survival (*B*) and overall survival (*C*) of patients treated with adjuvant ADT vs control group.