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HORMONAL TREATMENT BEFORE RADICAL PROSTATECTOMY: A 3-YEAR FOLLOWUP

GUNNAR AUS, PER-ANDERS ABRAHAMSSON, GÖRAN AHLGREN, JONAS HUGOSSON, SVEN LUNDBERG, MODDY SCHAIN, SONNY SCHELIN AND KNUD PEDERSEN

From the Departments of Urology, Göteborg University, Göteborg and Lund University, Malmö, and Departments of Surgery, County Hospital, Kristianstad, and County Hospital, Kalmar, and Departments of Pathology and Surgery, County Hospital, Jönköping, Sweden

ABSTRACT

Purpose: Hormonal treatment administered before radical prostatectomy has been shown to decrease the rate of positive surgical margins. We determine whether preoperative hormonal treatment has any impact on the subsequent failure rate.

Materials and Methods: We prospectively evaluated 122 patients with stages T1bNxM0 to T3aNxM0, grades 1 to 3 prostate cancer, including 64 randomly assigned to immediate radical retropubic prostatectomy and 58 randomly assigned to radical retropubic prostatectomy preceded by 3 months of pretreatment with a gonadotropin-releasing hormone agonist. We performed intention to treat analysis on the data with failure defined as lymph node involvement, serum prostate specific antigen greater than 0.5 ng./ml., or the need for postoperative hormonal or radiation adjuvant treatment.

Results: The positive margin rate was 23.6 versus 45.5% in the pretreatment plus prostatectomy versus prostatectomy only groups ($p = 0.016$). There were 20 failures (34.5%) in the pretreatment plus prostatectomy subgroup and 26 (40.6%) in the prostatectomy only group ($p = 0.48$). A negative surgical margin was associated with a significantly lower risk of progression than a positive surgical margin (20.8 versus 50.0%, $p = 0.0016$), and progression was delayed by approximately 1 year after hormonal pretreatment. However, at a median followup of 38 months there was no difference in progression-free survival ($p = 0.57$).

Conclusions: Although hormonal pretreatment significantly decreased the positive margin rate, it did not result in any difference in progression-free survival when followup exceeded 3 years. Thus, our current results do not support the routine administration of hormonal treatment before radical prostatectomy.

KEY WORDS: prostate, prostatic neoplasms, antiandrogens, gonadotropin-releasing hormone

Since radical prostatectomy was introduced as treatment for presumably localized prostate cancer at the beginning of this century, surgeons have attempted to overcome the problem of positive surgical margins. After it was recognized that prostate cancer is sensitive to hormonal manipulation, this treatment was used preoperatively to enable the excision of locally advanced tumors. In these early series some patients had long-term tumor-free survival.[1]

The development of gonadotropin-releasing hormone agonists and antiandrogens provided the possibility of reversible androgen blockade, which was given as 3-month pretreatment before radical prostatectomy. In some reports of small nonrandomized series in the literature comparison was made with historical patients who underwent surgery without pretreatment.[2–5] In these series prostate volume decreased and serum prostate specific antigen (PSA) dramatically decreased. Compared with historical controls there also seemed to be a decrease in the frequency of positive surgical margins.[3,5] Monfette et al reported decreased blood loss and operative time,[3] whereas Macfarlane et al noted no such effects.[4]

Based on these findings randomized studies were begun to compare radical prostatectomy with versus without hormonal pretreatment. Results revealed a statistically significant decrease in positive surgical margins after hormonal pretreatment but blood loss and operative time were unaffected.[6–8] Villers et al reported that a tumor-free surgical margin is associated with a low rate of PSA relapse in patients who undergo prostatectomy without hormonal pretreatment.[9] The prognostic value of a tumor-free margin after hormonal pretreatment is unknown.

There is general consensus that increased serum PSA after radical prostatectomy indicates residual disease and may serve as a sensitive surrogate end point in the followup of surgically treated patients. However, it has previously been shown that serum PSA after hormonal treatment does not reflect the actual tumor burden.[10] Thus, the rate of early PSA failure may be a difficult end point to interpret after hormonal pretreatment, because PSA is decreased by hormonal treatment. Therefore, it may be difficult to assess the true clinical effect of hormonal pretreatment with commonly used surrogate end points, such as the presence or absence of positive surgical margins, or serum PSA at short-term followup. We performed a randomized multicenter study to compare the outcome of radical prostatectomy with and without hormonal pretreatment at a mean 38-month followup.

MATERIALS AND METHODS

In our prospective randomized multicenter study 126 patients with stages T1bNxM0 to T3aNxM0 prostate cancer were recruited between December 1991 and March 1994, and randomly assigned to undergo immediate radical retropubic prostatectomy or prostatectomy after 3 months of hormonal

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pretreatment. Hormonal therapy consisted of 3.75 mg. triptorelin given intramuscularly every fourth week and a 3-week course of 50 mg. cyproterone acetate twice daily for disease flare protection. Four patients who did not undergo surgery were withdrawn from analysis and, thus, data on 122 (64 who underwent prostatectomy only and 58 who underwent pretreatment plus prostatectomy) were available for intention to treat analysis.

All surgical specimens were inked and examined as whole mount step sections by a pathologist (S. L.) blinded to treatment. Specimens were classified as margin negative (specimen confined) or margin positive (nonconfined). Treatment failure was defined as positive lymph nodes at histopathological examination (including frozen section), serum PSA greater than 0.5 ng./ml. at followup, and/or the initiation of postoperative adjuvant hormonal or radiation treatment. The latter alternative was included because in 5 cases adjuvant treatment was given before postoperative serum PSA reached the threshold level of 0.5 ng./ml.

Certain precautions are essential when analyzing randomized studies, particularly when hormonal pretreatment is involved. There must be strict adherence to intention to treat analysis if there is a chance that lymph gland metastases may be present. Otherwise erroneous and biased results may be obtained due to the effect of hormonal treatment, lymph node metastases may be assumed from the histopathological diagnosis, causing an imbalance between subgroups if analysis is confined to node negative cases. For example, of 20 patients scheduled to undergo prostatectomy, including 5 with node positive disease and 15 who underwent prostatectomy, treatment may fail in 6 of the 15 (40% failure), while in 20 who were scheduled to underwent pretreatment and prostatectomy, including 2 with node positive disease and 18 who underwent prostatectomy, treatment may fail in 9 of the 18 (50% failure). When randomization is successful, an equal number of lymph node metastases is anticipated in each subgroup. Thus, in the pretreatment plus prostatectomy subgroup 3 (5 − 2) of the 18 patients are expected to have occult lymph node metastases undiagnosed at routine histopathological examination, which indicates that there are more aggressive tumors in the 18 pretreatment plus prostatectomy patients than in the 15 prostatectomy only patients. If intention to treat analysis is performed, this imbalance is corrected, although numerically higher failure rates are obtained: 55% or (5+6)/20 for prostatectomy and 55% or (2+9)/20 for pretreatment plus prostatectomy.

We performed the Mann-Whitney signed rank test to compare subgroups in regard to time to failure, and the chi-square test to assess the risk of failure in relation to positive and negative surgical margins. With cases that had not failed as censored observations we used Kaplan-Meier curves to describe progression-free survival, and we compared differences using the Mantel-Cox log rank test.

RESULTS

Lymph node metastasis was noted in 12 of the 122 men, including 9 of the 64 in the prostatectomy only group and 3 of the 58 in the pretreatment plus prostatectomy group (14 versus 5%, p = 0.09). Thus, prostatectomy and surgical margin evaluation were performed in 110 patients 50 to 77 years old (mean age 66.5) with node negative disease. In the surgery only and surgery plus pretreatment groups 64 and 35% of the patients, respectively, had moderately or poorly differentiated tumors, while only 1 (1%) had a well differentiated tumor. Pretreatment serum PSA was 0.8 to 190 ng./ml. (median 11.4). The 2 subgroups were comparable in regard to patient age, serum PSA, clinical stage and grade distribution (table 1). Followup was 5 to 60 months (mean 38.3, median 38.0) in patients in whom treatment had not already failed. Only 6 patients were followed for less than 2 years, including 3 who died of unrelated causes 5 to 14 months postoperatively.

TABLE 1. *Baseline data of patients who underwent radical prostatectomy*

Variable	Pretreatment + Prostatectomy	Prostatectomy Only
No. pts.	55	55
Mean age (range)	67 (50–77)	66 (54–73)
Median PSA (ng./ml.):	11.3	11.0
0–10	24	27
10–20	18	20
20–50	12	8
Greater than 50	1	0
T stage:		
1b–c	10	15
2a–b	9	9
2c–T3a	36	31
Gleason grade*		
2–4	0	1
5–7	34	36
8–10	17	18

* Impossible to determine by core biopsy in 4 patients.

The rate of positive margins was significantly lower for pretreatment plus prostatectomy than for prostatectomy only (13 of 55 men, 23.6% versus 25 of 55, 45.5%, p = 0.016). At histopathological evaluation seminal vesicle involvement was noted in 8 of 55 pretreatment versus 12 of 55 prostatectomy only cases (14.5 versus 21.8%, p = 0.32). Three patients who received pretreatment had node positive disease and another 17 had subsequent failure, while 9 who underwent prostatectomy only had node positive disease and 17 had subsequent failure. Overall there was failure in 20 pretreatment plus prostatectomy and 26 prostatectomy only cases (34.5 versus 40.6%, p = 0.48.). Time to failure was longer after hormonal treatment (table 2). Almost all failures were biochemical with an increased serum PSA level (table 3). Despite the longer time to failure after hormonal pretreatment there was no difference in progression-free survival after the median 38 months of followup was achieved (see figure).

Evaluation of the patients with node negative disease (those who actually underwent radical prostatectomy) revealed that specimen confined disease (negative margins) was associated with a significantly lower risk of progression during the relatively brief followup (table 4). The slightly higher failure rate in patients in the specimen confined and margin positive subgroups who received pretreatment was probably due to lymph node metastasis that may have been masked by hormonal treatment. This interpretation is supported by the fact that the failure rate in the subgroup with margin positive disease is comparable when node positive disease is considered (table 4).

DISCUSSION

Pretreatment with a gonadotropin-releasing hormone agonist for 3 months before radical prostatectomy resulted in a

TABLE 2. *Time to progression after radical prostatectomy in 46 patients*

Time	No. Pretreatment + Prostatectomy	No. Prostatectomy Only
Node pos.	3	9
Mos.:		
Less than 3	0	9
4–12	6	2
13–24	3	3
25–36	4	0
Greater than 37	4	3
Total No. (mean mos.*)	20 (23.9)	26 (12.8)

* Excluding node positive patients (p = 0.018).