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Neoadjuvant Hormonal Therapy Prior to Radical Prostatectomy: Evaluation of Pathological Downstaging and Biochemical Relapse

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Abstract

Objectives: The effect of neoadjuvant hormonal therapy (NHT) prior to radical prostatectomy (RP) on pathological downstaging of prostate cancer and biochemical relapse of serum prostate specific antigen (PSA) level was evaluated.

Materials and Methods: Twenty selected patients with prostate cancer, who were treated with hormonal therapy and demonstrated biochemical downstaging by reduction of PSA prior to RP and bilateral pelvic node dissection at the Tohsei National Hospital between January 1997 and August 2001, are reported on. The complete RP specimens of these 20 men were used for accurate evaluation of the pathological stage. All 20 patients received NHT; ten patients were treated with leuprolide plus flutamide and 10 received leuprolide plus chlormadinone acetate (CMA).

Results: Decreases in serum PSA values were demonstrated from a pre-hormonal average of 49.7 ng/m*l* to an average of 0.52 ng/m*l* after NHT. Of the three clinical stages, A2-C, for cancer patients, two of the 20 patients had stage A2, two had stage B1, nine had stage B2, and seven had stage C. Of the 20 patients with biochemical downstaging, two had pathological stage B1, seven had pathological stage B2, eight had pathological stage C, and three had positive pelvic lymph nodes. Ten (50%) of the 20 patients were reported to have positive surgical margins. Seminal vesical extension was observed in two cases, and penetration was not observed. Positive nodes were identified in three (15%) patients. Among the seven clinical stage C patients, one had pathological stage B1 disease and two had pathological stage B2. Four of nine patients with clinical stage B2 prostatic cancer had pathological stage C disease. The actuarial incidence of a rising PSA at 3 years for the leuprolide plus CMA group was 28.9% compared with 37.5% for the group receiving leuprolide plus flutamide. The cases of biochemical relapse did not necessarily indicate a high stage and had no tendency to be high for baseline PSA level, positive margin rates or Gleason scores.

Conclusions: A significant decrease in the rate of penetration could be observed after NHT, though it was not so effective for pathological downstaging, and changes in the preoperative PSA level did not predict those patients who might have a favorable result.

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Key words: prostate cancer, neoadjuvant hormonal therapy, radical prostatectomy

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Introduction

The hormonal dependence of prostate cancer was first discovered in 1941[1], and the dramatic effects of androgen withdrawal on tumors have since been documented often. Therefore, many urologists pursued combination therapy prior to radical prostatectomy to downstage prostate cancer in men with locally advanced disease[2-4]. Thus, neoadjuvant hormonal therapy (NHT) was used for more than a decade for prostate cancer[2-6]. However, it fell out of favor for several reasons, including the side-effects of estrogen therapy, the finality of castration, improved staging methods, and newer treatment strategies for prostate cancer. Contemporary interest in NHT has resurfaced primarily as a result of the introduction of total androgen blockade. With these reasons in mind, we investigated the possibility of treating prostate cancer better by using NHT prior to radical prostatectomy.

Materials and Methods

Between January 1997 and August 2001, 20 men with adenocarcinoma of the prostate consented to participate in this investigation and to provide surgical specimens. None of the patients had had prior hormonal therapy. Only those patients with previously untreated, histologically confirmed clinical stage A2, stage B1, stage B2, and stage C prostate cancer were eligible for enrolment. The patients were staged before NHT by digital rectal examination (DRE), transrectal ultrasound (TRUS), computed tomographic scanning (CT), magnetic resonance imaging (MRI), serum prostate specific antigen (PSA), and bone scanning.

Following NHT, all patients underwent radical prostatectomy and pelvic lymph node dissection. They received NHT for an average of 3.7 months (range 2.0 – 5.7 months) prior to radical prostatectomy. All patients were treated with a luteinizing hormone-releasing hormone (LHRH) agonist (leuprolide, 3.75 mg intramuscularly every 28 days) plus flutamide (odyne, 250 mg orally three times a day), or LHRH agonist plus chlormadinone acetate (CMA) (prostal, 50 mg orally twice a day) prior to radical prostatectomy. Ten patients were treated with leuprolide plus flutamide and 10 received leuprolide plus CMA.

The normal range of serum PSA was 0.0 to 4.0 ng/m*l*, and the level of PSA in serum samples was measured using the radio immunoassay performed on the TANDEM-R. The serum PSA value was determined for each patient before and at the conclusion of NHT, and just prior to radical prostatectomy, after which serum PSA was measured every 3 months as a follow up. Those men who obtained reduction of PSA levels following NHT were deemed to have biochemical downstaging. Subsequently, to be considered biochemically free from disease, a patient had to have no clinical, radiographic, or biochemical evidence of recurrent disease in the period of the investigation. Biochemical relapse after prostatectomy was defined as any detectable level of PSA.

All prostate specimens, classified into the juxtaposition stump and the distal stump, were evaluated histologically for penetration or capsular invasion, surgical margins, seminal vesical extension, Gleason score and lymph nodes. Moreover, there were no findings of incomplete excision for prostatic apex. The prostate specimens were fixed and radially sectioned in 5-mm whole-mount segments from the apex to the base and submitted in their entirety for histopathologic examination. After that, pathological stage and Gleason score were compared with clinical data. Actuarial survival curves were generated using the Kaplan-Meier method, and Wilcoxon's test was applied to determine statistical significance.

Results

The characteristics of the patients who took part in this investigation are listed in **Table 1**. Patient age ranged between 54 and 81 years (median 67 years). The average baseline PSA level prior to NHT was 49.7 ng/m*l* (range 9.0 to 170.1 ng/m*l*). Of the 20 patients, two had pathologically confirmed stage A2 disease, two had stage B1 disease, nine had stage B2 disease, and seven had stage C disease.

Table 1 Patient characteristics (pretreatment)

Age (yr)	
Median	67
Range	54—81
Baseline PSA (ng/ml)	
Average	49.7
Range	9.0—170.1
Clinical stage	
A2	2 (10%)
B1	2 (15%)
B2	9 (50%)
C	7 (25%)
Gleason score	
2— 4	3 (15%)
5— 7	10 (50%)
8—10	5 (25%)
Indeterminate	2 (10%)

PSA, Prostatic specific antigen;

Table 2 Patient characteristics (after neoadjuvant hormone therapy)

Serum PSA (ng/ml)	
Average	0.52
Range	0.2—5.3
Pathological stage	
B1	2
B2	7
C	8
D1	3
Margin status	
Negative	10
Positive	10
juxtaposition stump	10
distal stump	0
Seminal vesical extension	2
Penetration	0
Lymph node metastases	
Negative	17
Positive	3

PSA, Prostatic specific antigen;

Prior to NHT, the distribution of 2–4, 5–7, and 8–10 Gleason scores was 15%, 50%, and 25%, respectively. In two cases, Gleason scores could not be established because of insufficient tissue to assign both a major and a minor Gleason pattern.

The patient characteristics after NHT are listed in **Table 2**. Prior to radical prostatectomy, biochemical downstaging was documented in all patients. Decreases in serum PSA values were demonstrated from a pre-hormonal average of 49.7 ng/ml to an average of 0.52 ng/ml after NHT. Of the 20 patients with biochemical downstaging, two had pathological stage B1 disease, seven had pathological stage B2 disease, eight had pathological stage C disease, and three had positive pelvic lymph nodes. Negative margins of resection were obtained in 50%. Ten (50%) of the 20 patients were reported to have positive surgical margins, of which all were located in juxtaposition. Although seminal vesical extension was observed in two cases, penetration was not observed. Positive nodes were identified on permanent section in three (15%) patients. Among the seven clinical stage C patients, one had pathological stage B1 disease and two had pathological stage B2. Four of nine patients with clinical stage B2 prostatic cancer had pathological stage C disease. The average Gleason scores from pre-hormonal biopsies were identical to those of postsurgery pathological specimens. Of the three patients with pathological downstaging the Gleason score was the same in two patients and had decreased in one (data not shown).

Thus, only three of the 20 patients demonstrated pathological downstaging from the clinical stage. Although there was no difference between the groups in terms of 3-year biochemical survival, the actuarial incidence of a rising PSA at 3 years for the leuprolide plus CMA group was 28.9% compared with 37.5% for the group receiving leuprolide plus flutamide (**Fig. 1**). Among both subgroups, there was no bias demonstrated by patient age, baseline PSA level, clinical tumor stage or Gleason score, as shown also in **Table 3**. The cases of biochemical relapse did not necessarily indicate a high stage and had no tendency to be high for baseline PSA level, positive margin rates or Gleason scores (**Table 4**).

Two patients experienced treatment-related morbidity. One patient was treated for MRSA infection following radical prostatectomy. The other man developed urethral stenosis, which was treated successfully with dilatation by catheterization. None required any dosage reduction of hormonal agents because of adverse events.

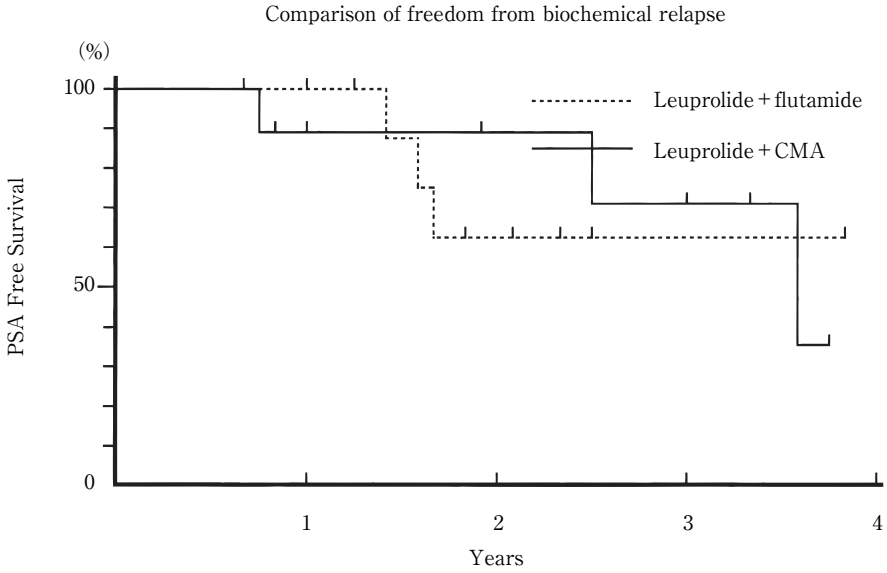

Fig. 1 Comparison of freedom from biochemical relapse among patients treated with neoadjuvant hormonal therapy (Leuprolide + CMA versus Leuprolide + flutamide prior to radical prostatectomy). PSA, prostatic specific antigen; CMA, chlormadinone acetate

Table 3 Comparative age, baseline PSA, clinical tumor stage and Gleason score before NHT

	Leuprolide + CMA	Leuprolide + flutamide
Age (yr)		
Median	69	68
Range	58—81	54—74
Baseline PSA (ng/ml)		
4—19.9	3	2
20—99.9	5	7
＞100	2	1
Clinical tumor stage		
A2	1	1
B1	1	1
B2	4	5
C	4	3
Gleason score		
2—4	0	3
5—7	6	4
8—10	4	1
Indeterminate	0	2

PSA, Prostatic specific antigen; NHT, Neoadjuvant hormonal therapy; CMA, Chlormadinone acetate;

Table 4 Comparative baseline PSA, clinical tumor stage, margin status and Gleason score before NHT

	PSA free	Biochemical relapse
Baseline PSA (ng/ml)		
4—19.9	3	2
20—99.9	8	4
＞100	3	0
Clinical tumor stage		
A2	2	0
B1	0	2
B2	6	3
C	6	1
Margin status		
Negative	7	3
Positive	7	3
Seminal vesical extension	1	1
Gleason score		
2—4	1	2
5—7	7	3
8—10	4	1
Indeterminate	2	0

PSA, Prostatic specific antigen; NHT, Neoadjuvant hormonal therapy

Discussion

Neoadjuvant hormonal therapy is an old concept that has recently been revisited[7]. The advantages of NHT are tumor downstaging, which causes less tumor implantation from showering tumor cells during surgery. Conversely, the disadvantages include a delay in surgery resulting in possible metastatic spread, increased psychological stress on the patient, and the side-effects of hormonal therapy. It is well recognized that with androgen deprivation

the prostate undergoes cellular atrophy but not cell death. To expect pathological downstaging, cancer cells that have already penetrated through the prostatic capsule would have to be sucked back into the prostatic gland.

In our study, only three of the 20 patients (15%) demonstrated pathological downstaging from the clinical stage. Although clinical staging accuracy is traditionally poor between Stage B and stage C, the possibility of overstaging is low, because of the staging of all patients by DRE, TRUS, CT, MRI, and bone scanning before NHT. In consideration of references, positive margin rates of 30% to 60% are reported following radical prostatectomy[8,9]. Lopez C et al. reported that the Gleason score remained unchanged in one and increased in the other[10]. There is also another report that NHT did not improve positive margin rates of clinical stage C tumors[11]. In the present analysis, no beneficial effects of NHT for improvement of positive margin rates or Gleason score were observed. We think that NHT was still effective in sucking extracapsular cancer cells back into the prostatic gland, because there were no cases of penetration even though there were seven clinical stage C cases. Moreover, downsizing of the prostate can be expected generally in almost all patients following NHT[12]. Therefore, even if NHT dose not improve positive margin rates, we can expect the prostate glands to become movable and facilitate surgical removal following NHT, sucking extracapsular cancer cells back. Among the three patients with pathological downstaging, an average PSA level of 23.1 ng/m*l* before NHT was noted. The patient with the greatest decrease (170 ng/m*l* reduction) had pathological stage D1 disease. These data would suggest that despite the continued presence of prostatic epithelial cells, serum PSA levels are dependent on androgenic stimulation. Moreover, it is recognized that the initial rapid decline in PSA is because of cessation of androgen-regulated PSA gene expression[13,14]. We suppose that since NHT did not contribute to improvement of positive margin rates, it could not complete pathological downstaging in spite of decreased PSA levels. In this study, there was no correlation between preoperative changes in PSA levels and pathological outcome after surgery. However, changes in serum PSA levels during NHT provide objective biochemical information to gauge tumor response and to identify patients not responding favorably. PSA-free was obtained with our case of high baseline PSA level, when tumor response for NHT was favorable.

The most important point, in the end, is whether NHT reduces PSA recurrence rates. Corn et al. reported that only a low baseline PSA independently predicted the likelihood of remaining biochemical free of disease[15]. However, this likelihood could not be predicted by baseline PSA level, clinical tumor stage, margin status, or Gleason score in our present study. Freedom from biochemical relapse rate at 3 years for the entire series was 63.8%. Although there was a suggestion of an early advantage in the use of leuprolide plus CMA rather than leuprolide plus flutamide prior to radical prostatectomy, no significant differences in rates of freedom from biochemical relapse were observed (**Fig. 1**). In the present analysis, hormonal agents did not distinguish which patients were likely to benefit from NHT.

In conclusion, a significant decrease in the rate of penetration could be observed after NHT, though it was not so effective for pathological downstaging. Moreover, changes in the preoperative PSA level did not predict those patients who might have a favorable result.

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