

## LONG-TERM RESULTS OF NEOADJUVANT HORMONAL THERAPY PRIOR TO RADICAL PROSTATECTOMY IN PATIENTS WITH CLINICALLY LOCALIZED PROSTATE CANCER: BIOCHEMICAL AND PATHOLOGICAL EFFECTS

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The objective of this study was to evaluate the long-term biochemical and pathological effects induced by neoadjuvant hormonal therapy (NHT) in patients with clinically localized disease. Between March 1993 and May 1997, 24 patients with clinically localized prostate cancer received NHT for 3 to 11 months (median: 5 months) using luteinizing hormone-releasing hormone analogue prior to radical prostatectomy and pelvic lymphadenectomy. The clinical stage was T1 in 1 patient, T2 in 17 and T3 in 6, the pretreatment serum prostate-specific antigen (PSA) value was  $\leq 10$  ng/ml in 5 patients, 10 to 20 ng/ml in 4 and  $>20$  ng/ml in 15 (mean:  $34.7 \mu\text{g/l}$ ), and the Gleason score was  $\leq 4$  in 9 patients, 5 to 7 in 11 and  $>8$  in 3. The mean prostate specific antigen (PSA) value 3 months after NHT had reduced below 2 ng/ml in 18 of the 24 patients (67%), and finally decreased by an average of 95% (*i.e.*, 1.9 ng/ml) prior to surgery. The pathological stage was pT0 in 2 patients, pT2 in 10 and pT3 in 12. The incidence of organ-confined disease (OCD) was significantly higher in patients with clinical stage T1 or T2a than with T2b or T3, with pretreatment PSA values  $\leq 10$  ng/ml than with PSA values  $>10$  ng/ml, and with PSA values  $\leq 2$  than with PSA values  $>2$  at 3 months after NHT; in contrast, the Gleason score had no significant impact on the rate of OCD. After a median follow-up of 49 months (range 34 to 85 months), 6 patients (25%) had a recurrence evidenced by rising PSA, and the 3-year recurrence-free survival rate was 79%. These results suggest that NHT appears not to be of significant additional benefit to patients who have a higher clinical T stage, higher pretreatment PSA values and/or in patients whose PSA values do not normalize early in the treatment process.

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**Key words:** Prostate cancer, Neoadjuvant hormonal therapy, Prostatectomy, PSA

### INTRODUCTION

Radical prostatectomy is widely performed to treat patients who have localized prostate cancer, and the number of radical prostatectomies is increasing owing to earlier detection of organ confined disease with advance of diagnostic procedures. However, despite earlier detection and improved surgical techniques, the incidence of positive surgical margins remains high, ranging from 30 to 60%<sup>1,2)</sup>. Unfortunately, patients with incompletely resected prostate cancer are at significantly increased risk for local recurrence and/or distant metastasis<sup>1)</sup>. In addition, preoperative clinical staging systems are unable to select patients with pathologically organ-confined diseases (OCD); that is, despite the association between a higher pathological stage and several factors, including the preoperative prostate specific antigen (PSA) level and tumor grade, to date, no prognostic variable exists that could be applied independently to predict pathological stage accurately<sup>3,4)</sup>.

Neoadjuvant therapy is defined as a systemic therapy that is administered after the diagnosis of cancer but before definitive locoregional therapy has started. In prostate cancer, the development of potent, well-tolerated and reversible agents for androgen withdrawal therapy provides a safe way for inducing tumor regression in an attempt to downstage the tumor and decrease the incidence of positive surgical margins; however, the efficacy of neoadjuvant hormonal therapy (NHT) for prostate cancer remains controversial<sup>5)</sup>. To date, several randomized studies have demonstrated the ability of NHT to decrease tumor volume and the incidence of margin-positive rates<sup>6–9)</sup>. However, whether NHT decreases the risk of disease recurrence has not been well assessed because of lack of long-term follow-up.

In the present study, we summarized the long-term results of NHT prior to radical prostatectomy in 24 patients with clinically localized prostate cancer, and retrospectively analyzed the biochemical and pathological effects of NHT.

### PATIENTS AND METHODS

Between June 1993 and August 1997, 24 patients with previously untreated, histologically confirmed clinical stage T1, T2 or selected T3 tumors received NHT followed by radical prostatectomy and pelvic lymphadenectomy<sup>10)</sup> at Kobe University Hospital. The diagnostic and staging procedures included digital rectal examination (DRE), transrectal ultrasonography, serum PSA assays (Tosoh, Tokyo, Japan), transrectal biopsies under the guidance of ultrasound, pelvic computed tomography and a bone scan. Clinical data were obtained from the retrospective review of all medical records, and pathological examination was performed by a single pathologist. Clinical and pathological stages were determined according to the 1992 TNM classification system<sup>11)</sup>

As a rule, patients were treated with luteinizing hormone-releasing hormone (LH-RH) analogue (leuprolide: Leuplin 3.75 mg monthly; or goserelin acetate: Zoladex 3.6 mg monthly) for at least 3 months (median: 5 months; range 3 to 11 months) prior to surgery, and assessed with DRE and serum PSA every 4 to 6 weeks until surgery. All patients underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy. All surgical specimens were fixed and sectioned at 5 mm thickness, then examined for positive margins, capsular penetration, seminal vesicle invasion, positive lymph nodes and tumor grade. If the pathological stage was pT3 or more, the surgical margin was positive, and/or lymph node metastasis was detected, adjuvant hormonal therapy was performed using an LH-RH analogue.

The median follow-up period for these 24 patients was 49 months (range 34 to 85 months). Patients were followed every three months postoperatively, and evaluated by DREs and serum PSA analyses. Biochemical recurrence was defined as increase in PSA exceeding 1 ng/ml two consecutive times<sup>10)</sup>. All survival data presented in this study were analyzed by the Kaplan-Meier technique using a log-rank test. Other data were evaluated by the chi-squared test. The level of significance was set at  $p < 0.05$ .

### RESULTS

The characteristics of the 24 patients involved in this study are shown in Table 1. Briefly, the clinical stage was T1 in 1 patient, T2a in 7, T2b in 9 and T3 in 7; the serum PSA was  $\leq 10$  ng/ml in 5 patients, 10 to 20 ng/ml in 4 patients and  $> 20$  ng/ml in 15; and the Gleason score was  $\leq 4$  in 9 patients, 5 to 7 in 12 and  $> 8$  in 3.

The mean level of serum PSA in these 24 patients upon diagnosis of prostate cancer was 34.7 ng/ml, but had decreased below 2 ng/ml in 18 of the 24 patients

Table 1. Clinical characteristics of 24 patients treated with neoadjuvant hormonal therapy

Characteristics	No. (%)
Median age (range) (years)	67 (48-77)
Clinical T stage (%):	
T1c	1 (4.1)
T2a	7 (29.2)
T2b	9 (37.5)
T3a	7 (29.2)
Grade (Gleason score)	
Well (2-4)	9 (37.5)
Moderately (5-7)	11 (45.8)
Poorly (8-10)	4 (16.7)
Serum PSA (ng/ml)	
$\leq 10$	5 (20.8)
10 to 20	4 (16.7)
$> 20$	15 (67.5)

(67%) after 3 months of NHT. Furthermore, the preoperative mean serum PSA value decreased by an average of 95% (*i.e.*, 1.9 ng/ml).

The pathological stage was pT0 in 2 patients, pT2 in 10 and pT3 in 12, and lymph node metastasis was detected in 2 of the 24 patients (8%). Compared to clinical T stage, 4 patients (17%) were pathologically downstaged by NHT, whereas up-staging was observed in 8 (33%). The incidence of OCD (*i.e.*, pT2 or less) was closely associated with the clinical T stage, pretreatment serum PSA value, and serum PSA value 3 months after NHT; however, the Gleason score in the biopsy specimens had no significant impact on the incidence of OCD (Table 2). Seven of the 8 patients (88%) with T1 or T2a tumors had OCD compared to 5 of the 16 (31%) with T2b or T3 disease ( $P < 0.005$ ). All 5 patients (100%) with pretreatment PSA values  $\leq 10$  ng/ml had OCCs, compared to 7 of the 19 (37%) with PSA values  $> 10$  ng/ml ( $P < 0.01$ ). None of the 6 patients (0%) with PSA values  $> 2$  ng/ml at 3 months after NHT had OCD, whereas 12 of the 18 (67%) with PSA values  $\leq 2$  ng/ml had OCD ( $P < 0.01$ ).

After a median follow-up of 49 months (range 34 to 85 months), 6 patients (25%) had a recurrence evidenced by rising PSA levels, and the 3-year recurrence-free survival rate was 79%. In addition, the biochemical recurrence-free survival rate did not correlate significantly with the pathological stage (Fig. 1).

### DISCUSSION

The ultimate goal of radical prostatectomy is complete removal of all cancer cells. Despite an improved ability to diagnose prostate cancer, accurate detection of OCD remains a challenge; that is, higher tumor stage, tumor grade and preoperative serum PSA value all correlate with a higher

Table 2. Association of pathological stage with several clinical factors

Pathological stage	No. (%)	No. Clinical T stage (%)				No. Pretreatment serum PSA (ng/ml) (%)				No. Serum PSA 3 months after NHT (ng/ml) (%)		No. Gleason score (%)		
		T1		T2		T3		T4						
		T1a	T1b	T2a	T2b	T3	T4	≤10	10 to 20	>20	≤2	>2	≤4	5 to 7
pT0	2 (8.3)	0 (0)	1 (14.3)	1 (11.1)	0 (0)	1 (20.0)	1 (25.0)	0 (0)	0 (0)	2 (11.1)	0 (0)	1 (11.1)	1 (8.3)	0 (0)
pT1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
pT2	10 (41.7)	1 (100)	5 (71.4)	2 (22.2)	2 (28.6)	4 (80.0)	1 (25.0)	5 (33.3)	10 (55.6)	0 (0)	0 (0)	2 (22.2)	7 (58.3)	1 (33.3)
pT3	12 (50.0)	0 (0)	1 (14.3)	6 (66.7)	5 (71.4)	0 (0)	2 (50.0)	10 (67.7)	6 (33.3)	6 (100)	6 (100)	6 (66.7)	4 (33.3)	2 (66.7)
Total	24	1	7	9	7	5	4	15	18	6	6	9	12	3

pathological stage, but none can be applied independently to predict the pathological stage<sup>12</sup>. As many as two thirds of clinically diagnosed OCD are understaged, and positive margin rates of 30 to 60% are reported after radical prostatectomy<sup>13</sup>. Not surprisingly, patients with extracapsular disease and/or positive surgical margins have a higher risk of disease recurrence<sup>14,15</sup>. Based on these findings, NHT prior to radical prostatectomy has been explored as a strategy to decrease tumor volume and the incidence of extraprostatic disease, as well as to treat micrometastatic disease.

Theoretically, the several advantages of NHT include the earlier induction of primary tumor regression with its undisturbed vascular bed and the simultaneous treatment of both the primary disease and any micrometastatic lesions, which suggests that NHT may allow for improved local control by subsequent surgery. In fact, several prospective randomized trials of NHT have been carried out, and have revealed that NHT reduced positive surgical margin rates by 20 to 40%<sup>6-9</sup>, however, it remains controversial whether NHT results in improved recurrence-free survival because of lack of long-term follow-up data.

In the present study, we retrospectively analyzed the long-term results of NHT prior to radical prostatectomy for patients with clinically localized prostate cancer. Although the mean value of serum PSA in the 24 patients decreased by more than 90% before surgery, the majority of these cases did not reach their PSA nadir before surgery. Gleave et al. reported that PSA levels do not become undetectable in 50% or more of patients with clinically localized prostate cancer treated by NHT for 3 months and that with microassay systems, the nadir may not occur for up to 8 or 9 months<sup>16</sup>. To date, the appropriate duration for NHT remains to be determined; however, judging from the biochemical effects of 3 months of NHT, a longer duration of NHT than 3 months might more effectively achieve the aforementioned objectives of NHT. In order to clarify the optimal period of NHT, the extension of NHT to 8 months or to the attainment of the PSA nadir is currently being explored by the Canadian Urologic Oncology Group and by the South-West Oncology Group.

The long-term follow-up data of randomized clinical trials are not yet available, but their preliminary results at 12 or 24 months of follow-up failed to demonstrate the differences in biochemical PSA failure rates between the groups with and without NHT<sup>5,9</sup>. Therefore, it is important to determine which patient group would be most likely to benefit from NHT. In this series, we showed that patients with clinical T1 or T2a tumors, with pretreatment serum PSA levels of  $\leq 10$  ng/ml, and/or

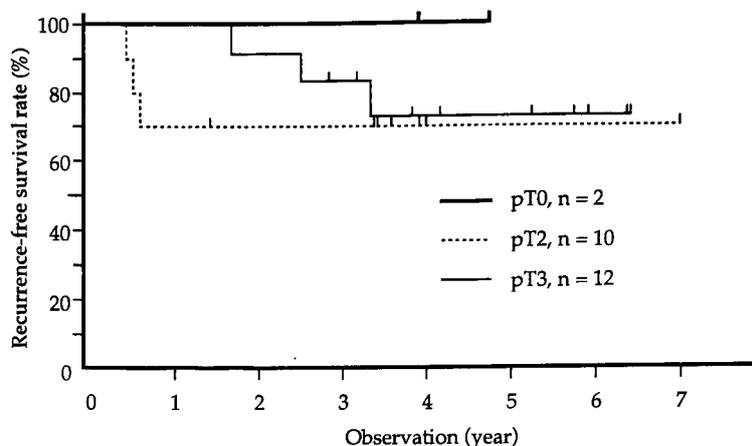


Fig. 1. Biochemical recurrence-free survival curves according to pathological stage. No statistically significant differences in the recurrence-free survival were observed in relation to pathological stage.

with serum PSA levels of  $\leq 2$  ng/ml at 3 months after NHT are more likely to have OCD, whereas the incidence of OCD did not significantly correlate with the Gleason score. However, several previous studies have reported that the risk of positive margins increased proportionally with increasing tumor grade, in addition to the clinical T stage and the pretreatment serum PSA level<sup>17,18)</sup> This discrepancy may be attributable to a lack of statistical power of this study to demonstrate such a difference.

Several factors may explain the absence of an apparent difference in PSA recurrence rates despite favorable changes in the rates of positive surgical margins by NHT: the pathologist can no longer easily determine the exact margin; the peripheral tumor cell population is more sensitive to androgen withdrawal; approximately half the patients in the previously reported studies had very low-risk tumors for PSA recurrence after radical prostatectomy; the sample population was limited in number and the follow-up period was not long enough to detect significant differences in biochemical recurrence rates. One further possibility is that patients who fail biochemically, whether they receive NHT or not, may simply represent a subgroup with aggressive tumors that may not respond to androgen ablation. In this series, no significant differences in the incidence of PSA recurrence were observed in relation to pathological stage. In addition, PSA recurrence was observed in 3 patients with OCD and 3 patients with extraprostatic diseases. Thus, NHT may be of no benefit to the promotion of recurrence-free survival and that the provision of adjuvant hormonal therapy for patients with pathological risk factors possibly reduces the risk of biochemical failure, therefore, it would be reasonable to consider radiation therapy rather than radical surgery for patients with non-OCD, since patients with non-OCD are not expected to achieve a similar prognosis to those with OCD, if

they do not receive adjuvant hormonal therapy.

Based on this long-term, albeit small-scale, study of the effects of NHT and radical surgery for patients with clinically localized prostate cancer, we conclude that NHT appears not to offer significant prognostic benefit in patients who have higher clinical T stages, higher pretreatment PSA values and/or in patients whose PSA values do not normalize early in the treatment process.

#### REFERENCES

- 1) Epstein JI: Incidence and significance of positive margins in radical prostatectomy specimens. *Urol Clin North Am* **23**: 651-663, 1996
- 2) Paulson DF: Impact of radical prostatectomy in the management of clinically localized disease. *J Urol* **152**: 1826-1831, 1994
- 3) Oesterling JE: Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* **145**: 907-923, 1991
- 4) Bengma CH, Kranse R, Blijenberg BG, et al.: The free-to-total serum prostate specific antigen ratio for staging prostate carcinoma. *J Urol* **157**: 544-547, 1997
- 5) Lee HH, Warde P and Jewett MA: Neoadjuvant hormonal therapy in carcinoma of the prostate. *BJU Int* **83**: 438-448, 1999
- 6) van Poppel H, de Ridder D, Elgamal AA, et al.: Neoadjuvant hormonal therapy before radical prostatectomy decreases the number of positive surgical margins in stage T2 prostate cancer: interim results of a prospective randomized trial. *J Urol* **154**: 429-434, 1995
- 7) Soloway MS, Sharifi R, Wajzman Z, et al.: Randomised prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B (T2bNxM0) prostate cancer. *J Urol* **154**: 424-

- 428, 1995
- 8) Goldenberg SL, Klotz L, Srigley J, et al. : Randomized, prospective, controlled study comparing radical prostatectomy alone and neoadjuvant androgen withdrawal in the treatment of localized prostate cancer. *J Urol* **156** : 873–877, 1996
  - 9) Goldenberg SL, Klotz L, Canadian Urologic Oncology Group : Randomized trial of neoadjuvant androgen ablation prior to radical prostatectomy : 24-month post-treatment PSA results. *Mol Urol* **2** : 165–169, 1998
  - 10) Klotz L, Gleave M and Goldenberg SL : Neoadjuvant hormone therapy : the Canadian trials. *Mol Urol* **4** : 233–238, 2000
  - 11) Schroder FH, Hermanek P, Dennis L, et al. . The TNM classification of prostate cancer. *Prostate* **4** : 129–138, 1992
  - 12) Gohji K, Nomi M, Egawa S, et al. : Detection of prostate carcinoma using prostate specific antigen, its density, and the density of the transition zone in Japanese men with intermediate serum prostate specific antigen concentrations. *Cancer* **79** : 1969–1976, 1997
  - 13) Zincke H, Oesterling JE, Blute ML, et al. : Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. *J Urol* **152** : 1850–1857, 1994
  - 14) Paulson DF : Impact of radical prostatectomy in the management of clinically localized disease. *J Urol* **152** : 1826–1831, 1994
  - 15) Epstein JI : Incidence and significance of positive margins in radical prostatectomy specimens. *Urol Clin North Am* **23** : 651–663, 1996
  - 16) Gleave ME, Goldenberg SL, Jones EC, et al. : Biochemical and pathological effects of 8 months of neoadjuvant androgen withdrawal therapy before radical prostatectomy in patients with clinically confined prostate cancer. *J Urol* **155** : 213–219, 1996
  - 17) Bonney WB, Schend AR, Timberlake D, et al. : Neoadjuvant androgen ablation for localized prostatic cancer : pathology methods, surgical endpoints and meta-analysis of randomized trials. *J Urol* **160** : 1754–1760, 1998
  - 18) Gleave ME, Goldenberg SL, Jones EC, et al. : Longer duration of neoadjuvant hormonal therapy prior to radical prostatectomy in clinically confined prostate cancer : biochemical and pathological effects. *Mol Urol* **1** : 199–205, 1997

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## 和文抄録

## 術前内分泌療法を施行した根治的前立腺全摘出術症例の臨床病理学的検討

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臨床的に限局性前立腺癌と診断し，術前内分泌療法に引き続き根治的前立腺全摘術を施行した24例を対象に臨床病理学的検討を行った。LH-RH アゴニストによる3カ月間の術前内分泌療法施行後，24例中22例においてPSAが $2\mu\text{g/l}$ 以下に低下し，術前には治療前平均値の約5%に低下した。臨床病期がT2a以下，治療前PSAが $10\mu\text{g/l}$ 以下。あるいは内分泌療法施行3カ月後のPSAが $2\mu\text{g/L}$ 以下の症例では，病理学的にもpT2以下であることが多かったが，Gleason

scoreとは相関しなかった。術後PSA failureを6例に認め，3年非再発率は79%であった（観察期間の中央値：49カ月）が，非再発率と病理学的病期との間には相関を認めなかった。以上より，臨床病期がT2b以上，治療前PSA値が $10\mu\text{g/l}$ を超える，あるいは内分泌療法施行3カ月後のPSA値が正常化しない症例においては，術前内分泌療法を施行しても病理学的にpT3以上である可能性が高いと思われた。

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