British Journal of Urology (1996), **78**, 432–436

A 3-year follow-up of patients with localized prostate cancer operated on with or without pre-treatment with the GnRH-agonist triptorelin

M. HELLSTRÖM, M. HÄGGMAN*, K. PEDERSEN†, C. BUSCH‡ and S. BRÄNDSTEDT

*Department of Urology, Danderyd Hospital, Karolinska Institute, Stockholm, *Department of Urology, University Hospital, Uppsala, †Department of Urology, County Hospital, Ryhov, Jönköping and ‡Department of Pathology, University Hospital, Uppsala, Sweden*

Objective To examine the effect of pre-operative androgen deprivation on the progression rate of malignancy in patients operated on for localized prostate cancer.

Patients and methods A total of 53 patients received no hormone therapy (group 1) and a further 38 patients (group 2) received the generic releasing-hormone agonist triptorelin during the 3 months before surgery. The patients in group 1 had T1b-T2 tumours, whereas 12 of those in group 2 had clinical stage T3 tumours. Despite this, the surgical specimens from the patients in group 2 showed a rate of cancer invasion of the surgical margins 20% lower than those from the patients in group 1. After prostatectomy, the patients were followed for 3 years by repeated analyses of prostate-specific antigen (PSA) in serum.

Results During the follow-up, the PSA level exceeded the upper threshold (0.6 ng/mL) in 16 % of the patients in group 1 and in 43 % of those in group 2 ($P < 0.05$). This difference was mainly related to the pre-treatment stage of the tumour. Some of the patients in group 1 received post-operative radiotherapy but this was not reflected in their PSA levels. Of the patients in group 1 and 2, 4% and 14% respectively ($P > 0.05$), developed symptoms from skeletal metastases.

Conclusion There was no evidence that pre-operative hormone therapy slowed the progression of prostate cancer.

Keywords Localized prostate cancer, neoadjuvant androgen deprivation, radical prostatectomy, prostate specific antigen, follow-up

Introduction

A serious limitation inherent in the surgical approach to localized prostate cancer is the high incidence (in some studies up to 60%) of unexpected tumour invasion through the margins of the surgical specimens [1–3]. Considering the androgen dependence of glandular and prostate cancer tissue, in 1944 Vallet [4] introduced pre-operative hormone ablation as a complement to prostatectomy. It has been suggested that such therapy improves the chances of eliminating the tumour by radical surgery [5,6].

In a previous study [7] we reported that temporary androgen deprivation was associated with a reduction in the glandular and tumour volumes. Moreover, it caused marked histopathological changes, such as cancer epithelial atrophy, a relative increase in the stroma in tumour areas, nuclear pyknosis, cytoplasmatic vacuolization and squamous metaplasia [8]. The present study reports the clinical findings at the 3-year follow-up of the patients referred to in [7] and of those in another series of patients [1] with localized prostate cancer, operated on without hormonal pre-treatment.

Accepted for publication 10 April 1996

Patients and methods

This retrospective investigation included only patients with localized prostate cancer and confirmed as having no regional or distant metastases. The patients who were not treated with hormones (group 1) were allocated to the study from September 1987 to April 1990 and those receiving hormone treatment (group 2) were recruited from July 1990 to March 1992. Post-operatively, the patients were re-investigated twice a year by clinical findings and the levels of serum PSA. Because the determination of PSA was only introduced as a routine assay after the start of the earlier investigation [1], no determinations were carried out in the patients in group 1 during the first part of the follow-up. Isolated increases in serum PSA were followed by repeated analysis of the levels until progress was verified. The study was interrupted in patients who developed skeletal metastases or a local recurrence, as verified by needle biopsy from the prostate bed, and also in patients with repeated blood

samples which showed elevated levels of PSA; under these conditions, patients received additional therapy. In group 1, the 53 patients (mean age 63 years, range 55–72) had been admitted to the Department of Urology, Uppsala University and were consecutive cases with stage T1b and T2 tumours (for definitions, see below). Patients with T3 tumours were offered radiotherapy and they were not included in this study. In five patients, the primary diagnosis of the tumour was made after TURP. One to three needle-core biopsies (1.2×20 mm, Biopty®, Bard, USA) were available from 32 patients; in 16, one to three fine-needle aspirates were used for pre-operative grading. Of 30 patients with positive surgical margins in the prostatectomy specimens, 13 were treated with full doses of post-operative irradiation (64–70 Gy). As such therapy is frequently associated with side-effects, mainly urinary incontinence, it was abandoned in the subsequent patients. At the follow-up, 49 patients were available for re-examination. Of the remaining patients, three had died because of intercurrent diseases and one had moved abroad.

Group 2 comprised 38 patients (mean age 62 years, range 49–72) who were recruited from the Departments of Urology at the University Hospital in Uppsala, at Danderyd Hospital, Stockholm, at Huddinge University Hospital, Stockholm and from the Department of Surgery at the County Hospital Ryhov, Jönköping. Patients with stage T1b, T2 and T3 tumours were included. Patients were admitted consecutively to the study, with one exception. Because it was also participating in another investigation, one hospital could provide only patients with T3 tumours. Before hormone therapy, from two to four ultrasound-guided needle-core biopsy specimens (1.2×20 mm, Biopty®) were taken in all cases and processed for histopathological analysis. Before surgery, androgen deprivation was achieved by giving three injections (3.75 mg monthly) of the GnRH-agonist triptorelin (Decapeptyl Depot®, Ferring AB, Malmö, Sweden). Testosterone levels were reduced to castration values in all 13 patients investigated; 35 patients participated in the follow-up. Two died because of intercurrent diseases and one was living abroad. Total retropubic prostatectomy with pelvic lymph node dissection was carried out using the technique of Walsh *et al.* [9].

Clinical staging was performed using a DRE supplemented by measurements from TRUS. With the classification system used [10], a T1b tumour was identified by examination of the material obtained at TURP in patients operated on because of bladder outlet obstruction, if $>5\%$ of the material examined consisted of cancerous tissue. A T2 tumour was defined as palpable and confined within the prostate, whereas a T3 tumour had extracapsular extension, as judged by the DRE. Among the patients in group 1, five had T1b tumours and 44 had T2 tumours (Table 1). In group 2, one patient had a T1b, 22 had T2 and 12 had T3 tumours. When re-examined by DRE after 3 months of hormone therapy, the tumour size was reduced in 22 of 35 cases [7]. The maximum tumour diameter measured by TRUS had decreased from a mean of 1.8 to 0.8 cm ($P<0.001$).

The prostate specimens obtained at surgery were characterized for pathological tumour stage (pT-stage). With the nomenclature used, stage pT2 comprised tumours entirely confined within the prostatic capsule. For only minor capsular penetration, the cancer was still considered to be specimen-confined (stage pT3–). The criteria for pT3+ tumours were extensive capsular penetration, invasion through the surgical margins or infiltration of the tumour into the seminal vesicles.

The distribution obtained by separating patients on the basis of the pT stage differed from that based on the clinical findings (Table 2). Thus, up to 60% of patients in group 1, compared with 40 % in group 2, had pT3+ tumours. The two groups of patients differed in the occurrence of pT2 tumours, which were more common in group 2. There was no apparent correlation between the occurrence of pT3 tumours and clinical stage T3 tumours.

Tumours were graded before treatment using a modification of the method described by Mostofi [11] and similar to that used by Böcking *et al.* [12]. Thus, both glandular differentiation and nuclear anaplasia were taken into account. With this method, three grades were distinguished (Table 1). There was no difference between patients in group 1 and 2 in the occurrence of grade 3 tumours (8% and 17%, respectively). The comparability

Table 1 Clinical tumour stage and grade in patients pre-treated without (group 1) or with (group 2) hormone on admission to the study

Stage	*Grade*	*Number*
Group 1		
T1b	G1	2
	G2	3
T2	G1	15
	G2	25
	G3	4
Total		49
Group 2		
T1b	G1	1
T2	G1	14
	G2	4
	G3	4
T3	G1	4
	G2	6
	G3	2
Total		35

Table 2 Distribution of the patients according to clinical (T-stage) and pathological tumour stage (pT-stage) in the prostatectomy specimens

	T1b	*T2*	*T3*	*Total*
Group 1 (not treated with hormone)				
pT2	0	8	–	8
pT3−	0	12	–	12
pT3+	5	24	–	29
Group 2 (treated with hormone)				
pT2	0	11	6	17*
pT3−	0	2	4	6
pT3+	1	9	2	12

*Significant difference ($P<0.01$) from group 1

of the grading specimens obtained by fine-needle and needle-core biopsies has been evaluated elsewhere [13].

The patients were followed for 3 years by two annual clinical examinations, including serum analyses of PSA. During the first part of the study, the Tandem-E® technique (Hybritech Inc, San Diego, CA, USA) was used to determine PSA. The Delfia® method (Pharmacia Wallacs, Turku, Finland) [14] was introduced in June 1992 and from then, all patients were assessed using the latter method. These procedures, both of which use two monoclonal antibodies, give virtually identical results [15].

During the follow-up of the prostatectomized patients, PSA levels of <0.6 ng/mL were taken to be within the control range [16]. Patients with levels exceeding this were considered to have residual or recurrent disease [16]. The chi-squared tests and Fisher's exact test were used to compare the groups.

Results

Most patients were in good health at the follow-up, although 4% of those in group 1 and 14% of those in group 2 ($P>0.05$) had developed symptoms from skeletal metastases. Three of five patients in group 2 initially had clinical stage T3 tumours. Local recurrences, as verified by needle biopsies from the prostate bed, were found in 4% of patients in group 1 and in 11% of those in group 2 ($P>0.05$). All patients with such complications had PSA levels >0.6 ng/mL and also had had tumours extending through the prostatic capsule on examination of the surgical specimens. PSA levels were determined in 11 patients in group 1 before surgery and they had a mean level of 13.7 ng/mL (range 2–40); in seven of these patients, the concentration of PSA was >10 ng/mL. Three months after surgery, one of them had a PSA level >0.6 ng/mL. Similar values were obtained in eight patients (16%) in group 1 during the follow-up.

PSA levels were evaluated from inclusion in all patients in group 2; before they were placed on medication, 16 of 35 had a serum PSA level >10 ng/mL. The mean level in the whole group was 15.9 ng/mL (range 1.2–68). Three months later, just before prostatectomy, the mean serum PSA level was 1.6 ng/mL (range 0.1–12.1) in 27 of 35 patients. A concentration of >10 ng/mL was detected in one patient with a T2 tumour, who showed no signs of a recurrence of the tumour during the follow-up. Three months after prostatectomy, the PSA level was >0.6 ng/mL in five of 35 patients (indicating residual cancer). Later, another 10 patients (33%) developed a similar rise in PSA level. Consequently, 15 of the 35 patients (43%) had PSA levels >0.6 ng/mL; once the PSA level began to rise, it continued to increase until radiation therapy or castration (hormonal or surgical) was performed.

The increase in PSA levels appeared to vary with the stage of the primary clinical tumour. Half the patients with T3 tumours had PSA concentrations above the threshold (Table 3). Considering the final tumour stage (pT-stage), it was possible to distinguish patients with pT2, pT3− and pT3+ tumours (Table 3). In all subgroups, PSA levels tended to be most elevated most frequently in patients who had undergone hormone therapy; the highest incidence (10 of 12) occurred in patients from group 2 with pT3+ tumours. There was an increase in PSA concentration in four of 11 and in six of eight patients with seminal vesicle involvement in group 1 and 2, respectively. The tumour grade of the biopsy specimens obtained pre-operatively showed no relation to the post-operative rise in PSA levels, although five of 10 patients with grade 3 tumours developed PSA levels >0.6 ng/mL. One of the 13 patients with pT3+ tumours who received immediate post-operative radiotherapy of the prostate bed showed elevated PSA levels during the follow-up, compared with four of 16 who received no such treatment.

Discussion

The endpoint in the present study was the level of serum PSA, commonly used as a marker for prostate cancer. PSA, a glycoprotein derived from prostate ductal and acinar epithelial cells [17], is organ- but not cancer-specific. Therefore, in non-prostatectomized patients, the serum PSA level may also be elevated in benign prostatic disease [18]. The synthesis of PSA is stimulated by androgen, as shown by a decrease in the serum level after castration [7]. After prostatectomy, the PSA level should be close to zero, if all cancerous and benign tissues have been removed [19]. Hence, any level of detectable PSA after prostatectomy may indicate that the tumour has persisted. It has also been shown, and

Table 3 Number of patients with elevated PSA levels during follow-up for clinical and pathological stage. The results are given in relation to the total number in each subgroup

	Total (n)	*Group 1 (n)*	*Mean PSA level (ng/mL [range])*	*Total (n)*	*Group 2 (n)*	*Mean PSA level (ng/mL [range])*
T1b	5	0	0	1	1	2.8
T2	44	8	7.5 (0.6–49)	22	7	2.6 (0.7–8.0)
T3	–	–	–	12	7*	4.4 (0.7–13)
pT2	8	0	–	17	2	–
pT3−	12	3	–	6	3	–
pT3+	29	5	–	12	10†	–

*$P<0.05$ from that found in all T1b and T2 tumours regardless of pre-treatment. †$P<0.001$ from that in group 1

is generally accepted, that patients with steadily increasing PSA levels eventually show evidence of persistent disease [20]. To avoid over-diagnosis, the upper control threshold after prostatectomy was set at 0.6 ng/mL [16].

When recruited to the follow-up study, the two groups of patients differed in tumour profile as none of those in group 1, but 12 of those in group 2 had T3 tumours. Presumably as a result of hormonal therapy, the tumour stages of the surgical specimens turned out to be more favourable in the patients in group 2. The larger proportion of organ-confined tumours in this group does not necessarily mean that the tumours had been downstaged, as other mechanisms could be of major importance. Thus, the hormone-induced reduction in glandular volume may have facilitated a more complete prostatectomy. Moreover, as a result of the profound histopathological changes achieved by androgen deprivation, malignant cells may have escaped detection [21].

Of the patients in group 1 and 2, 16% and 43%, respectively, had elevated PSA levels during the follow-up. This significant difference ($P<0.05$) may be related to the variations in pre-operative tumour stage (Table 2). After excluding patients with clinical stage T3 tumours, the difference in PSA relapse between the groups still tended to be high, although not significant.

The occurrence of high PSA levels was also related to the tumour stage of the prostatectomy specimens, which accords with the report of Stein *et al.* [22]. In the present study, two of 23 patients with pT2 tumours had serum levels of PSA >0.6 ng/mL ; similar levels occurred in six of 18 and 15 of 43 of the patients with pT3− and pT3+ tumours, respectively (Table 3). In patients with the same type of pT-stage, there tended to be consistently more elevated PSA levels in group 2, particularly if the patients had pT3+ tumours. Thus, it seems likely that the changes in the pT-stage achieved by hormone therapy were of minor importance for the long-term outcome.

The discrepancy in tumour grades may also contribute to variations in the post-operative PSA relapse [23]. However, patients in groups 1 and 2 could not be distinguished by the occurrence of G3 tumours in pre-operative biopsy specimens. Comparisons between prostatectomy specimens were not meaningful because of the histopathological changes caused by hormone therapy [8].

Another difference in the therapy between the groups was the post-operative irradiation given to 13 patients in group 1; although some patients may benefit from such therapy [24], no such effects were observed in the present study.

Temporary androgen deprivation in localized prostate cancer has been reported to reduce prostate volume and cause a marked decline in the serum PSA levels [6]. An improved local control after prostatectomy has been reported by some authors [5,25, 26] but not by others [27,28]. The present report showed that despite the marked effects of neoadjuvant hormone therapy on prostate volume and histopathology, and on PSA levels, there was no evidence of long-term benefits. A similar lack of positive results was observed by Cher *et al.* [27] who studied patients having stage C tumours which were treated with the LHRH analogue Depot Lupron® before prostatectomy.

In conclusion, there was no evidence that hormone therapy improved the long-term outcome in patients with localized prostate cancer. The possibility that neoadjuvant therapy has adverse effects cannot entirely be excluded. If the treatment has such effects, it may be through the stimulated growth of androgen-insensitive cell-lines [29,30]. Follow-up during longer randomized studies with more patients is needed to evaluate fully the benefits of pre-treatment with hormones before surgery

Acknowledgements

We thank Manuel de la Torre for examining the histological slides. We are grateful to Reinhard Stege and Hans Wijkström, Huddinge University Hospital, for providing us with tissue material and clinical data. We are also indebted to Professor Adam Taube, Uppsala University, for statistical advice. This study was supported by grants from the Johanna Hagstrand and Sigfrid Linnér Memorial Foundation.

References

1 Häggman M, Norberg M, de la Torre M, Fritjofsson Å, Busch C. Characterization of localized prostatic cancer. Distribution, grading and pT-staging in total prostatectomy specimens. *Scand J Urol Nephrol* 1993; **27**: 7–13

2 Stamey TA, Villers AA, McNeal JE, Link PC, Freiha FS. Positive surgical margins at radical prostatectomy: importance of the apical dissection. *J Urol* 1990; **143**: 1166–72

3 Epstein JI. The evaluation of radical prostatectomy specimens: therapeutic and prognostic implications. *Pathol Ann* 1991; **26**: 159–210

4 Vallett BS. Radical perineal prostatectomy subsequent to bilateral orchiectomy. *Delaware St Med J* 1944; **16**: 1–9

5 Tetu B, Srigley J, Boivin J-C *et al.* Effect of combination endocrine therapy (LHRH-agonist and flutamide) on normal prostate and prostatic adenocarcinoma. *Am J Surg Pathol* 1991; **15**: 111–20

6 Schulman CC. Neoadjuvant androgen blockade prior to prostatectomy: a retrospective study and critical review. *Prostate* Suppl 1994; **5**: 9–14

7 Häggman M, Hellström M, Aus G *et al.* Neoadjuvant GnRH-agonist treatment (triptorelin and cyproterone acetate for flare protection) and total prostatectomy. *Eur Urol* 1993; **24**: 456–60

8 Hellström M, Häggman M, Brändstedt S *et al.* Histopathological changes in androgen-deprived localized prostatic cancer. A study in total prostatectomy specimens. *Eur Urol* 1993; **24**: 461–5

9 Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function, anatomical and pathological considerations. *Prostate* 1983; **4**: 473–85

10 UICC. In Hermanek P, Sobin LH, eds, *TNM Classification of Malignant Tumours*, 4th Edition, Second Revision. New York, London, Paris: Springer, 1992

11 Mostofi FK. Grading of prostatic carcinoma. *Cancer Chemotherapy Rep* 1975; **59**: 111–7

12 Böcking A, Kiehn J, Heinzel-Wach M. Combined histologic grading of prostatic carcinoma. *Cancer* 1982; **50**: 288–94

13 Häggman M, de la Torre M, Norberg M, Busch C. Preoperative histological and cytological diagnosis and DNA ploidy assessments of localized prostatic cancer. *APMIS* 1994; **102**: 1–7

14 Lilja H, Christensson A, Dahlén U *et al.* Prostate-specific antigen in serum occurs predominantly in complex with alfa1-antichymotrypsin. *Clin Chem* 1991; **37**: 1618–25

15 Jacobsen SJ, Lilja H, Klee GG, Wright GL, Pettersson K, Oesterling JE. Comparability of the Tandem-R and IMx assays for the measurement of serum prostate-specific antigen. *Urology* 1994; **44:** 512–8

16 Hudson MA, Bahnson RR, Catalona WJ. Clinical use of prostatic specific antigen in patients with prostate cancer. *J Urol* 1989; **142**: 1011–7

17 Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate-specific antigen. *Invest Urol* 1979; **17**: 159–63

18 Oesterling JE, Jacobsen SJ, Klee GG *et al.* Free complexed and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios. *J Urol* 1995; **154**: 1090–5

19 Takayama TK, Lange PH. Radiation therapy for local recurrence of prostate cancer after radical prostatectomy. *Urol Clin North Am* 1994; **21**: 687–700

20 Lange PH, Ercole CJ, Lightner DJ *et al.* The value of serum prostate-specific antigen determinations before and after prostatectomy. *J Urol* 1989; **141**: 873–9

21 Smith DM, Murphy WM. Histologic changes in prostate carcinomas treated with leuprolide (luteinizing hormone-releasing hormone effect): distinction from poor tumor differentiation. *Cancer* 1994; **73**: 1472–9

22 Stein A, DeKernion J, Smith R, Dorey F, Patel H. Prostate-specific antigen levels after radical prostatectomy in patients with organ-confined and locally extensive prostate cancer. *J Urol* 1992; **147**: 942–6

23 Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer* 1993; **71**: 3582–93

24 Zietman AL. When should radiation therapy follow radical prostatectomy in the management of prostatic cancer? — Editorial. *Mayo Clin Proc* 1994; **69**: 700–1

25 Soloway MS, Sharifi R, Wajsman Z, McLeod D, Wood DP Jr, Puras-Baez A. Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer. *J Urol* 1995; **154**: 424–8

26 Van Poppel HP, 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* 1995; **154**: 429–34

27 Cher ML, Shinohara K, Breslin S, Vapnek J, Carrol PR. High failure rate associated with long-term follow-up of neoadjuvant androgen deprivation followed by radical prostatectomy for stage C prostatic cancer. *Br J Urol* 1995; **75**: 771–7

28 Oesterling JE, Andrews PE, Suman VJ, Zinke H, Myers RP. Preoperative androgen deprivation therapy: artificial lowering of serum prostate-specific antigen without downstaging the tumour. *J Urol* 1993; **149**: 779–82

29 Isaacs JT, Coffey DS. Adaptation versus selection as the mechanism responsible for the relapse of prostatic cancer to androgen ablation therapy as studied in the Dunning R-3327-H adenocarcinoma. *Cancer Res* 1981; **41**: 5070–5

30 Tribukait B. Nuclear deoxyribonucleic acid determination in patients with prostate carcinomas: clinical research and application. *Eur Urol* 1993; **23** (suppl. 2): 64–76

Authors

M. Hellström, MD, Senior Registrar.
M. Häggman, MD, Senior Registrar.
K. Pedersen, MD, Consultant Urologist.
C. Busch, MD, Consultant Pathologist, Associate Professor.
S. Brändstedt, MD, Consultant Urologist.
Correspondence: Dr M. Hellström, Department of Urology, Danderyd Hospital, Karolinska Institute, 182 88 Danderyd, Stockholm, Sweden.