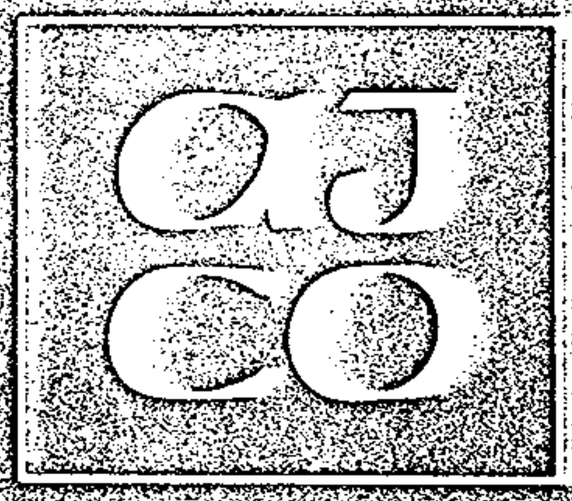
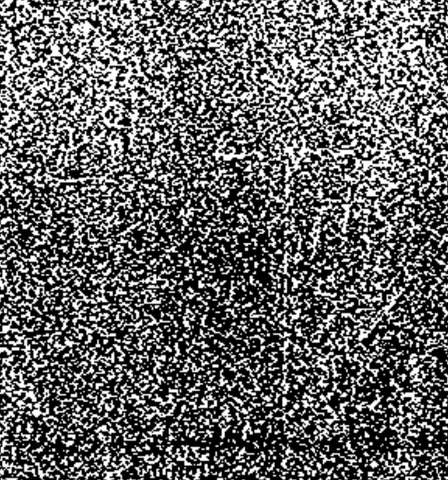
# American Journal of Clinical Oncology

CANCER CLINICAL TRIALS





New Treatment Modalities in Prostatic Cancer: LHRH Superagonists

Volume 11 Supplement 1 1988

**Luther W. Brady, M.D.** Editor-in-Chief

**RAVEN PRESS**

*Am J Clin Oncol (CCT) 11(Suppl. 1): S19–S28, 1988.*



# Treatment of Locally Advanced Prostatic Carcinoma With LHRH Analogues: Cytological, DNA–Cytophotometrical, and Clinical Results

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From June 1, 1981 to December 31, 1985, 122 patients aged 54 to 83 years, with locally advanced prostatic carcinoma, were treated with buserelin. Nineteen of the patients received combined therapy with buserelin and androcur for the first 3 months. To control the response of the primary tumor to therapy, fine-needle aspiration biopsy of the prostate was made in all patients at 3-month intervals. Fifty-eight (76.3%) of 76 patients with locally advanced prostatic carcinoma, with or without bone metastases, who underwent buserelin therapy for periods of 12–54 months showed good to satisfactory regression grades in the primary tumor. Eighteen patients (23.7%) showed poor regression or none, established by cytological findings and the measure of DNA by means of single cell-scanning cytophotometry. In three of the 58 patients, tumor progression or bone metastases occurred despite favorable regression grade; these were the only cases in which there was a discrepancy between the clinical course of the disease and the grade of regression in the primary tumor. According to TNM classification, 68 of the 78 patients treated for 12–54 months were in stage T3 NX M0; eight were in stage T3/T4 NX M1. On the basis of our long-term studies, it can be stated that buserelin therapy induces positive therapy response in more than 75% of locally advanced, inoperable, primary prostatic carcinoma. The clinical castration caused by buserelin through selective suppression of gonadotrophic secretion in the pituitary gland is, as the term implies, no more effective than surgical castration. However, the gonadotrophin suppression induced by buserelin is reversible and spares the patient the psychic stress of orchiectomy. This is a decisive advantage in light of the fact that in 20–40% of patients with locally advanced primary prostatic carcinoma. the primary tumor is hormone-refractory, and surgical castration would prove unnecessary after all.

**Key Words:** Locally advanced prostatic carcinoma—Buserelin therapy—Combined Buserelin and cyproterone acetate treatment—Therapy control—Cytology—DNA cytophotometry.

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A great variety of therapies is available for the treatment of locally advanced prostatic carcinoma with or without metastases. Hormone withdrawal in itself is not a new treatment approach; it has been practiced for many years in the forms of orchiectomy, estrogen or antiandrogen therapy, and irradiation. But now it can also be affected by applying the LHRH analogues of the endogenous decapeptide LHRH, isolated and synthesized by Schally in 1971 (2,3,5,11,12).

The therapeutic applicability of LHRH analogues derives from the effect they have on the pituitary gland. They desensitize this gland, and, with adequate dosage, reduce LH and testosterone production to the level found in surgically castrated men (9–11). It is still an open question whether the stimulation preceding suppression of gonadal function in the initial stage (first to second week) of therapy with LHRH analogues is clinically relevant. To prevent the short-term increase in testosterone production, various authors recommend simultaneous administration of a regular antiandrogenic drug such as cyproterone acetate (1,4,6).

## PATIENTS AND METHODS

At the Department of Urology of the Free University of Berlin, Charlottenburg Medical Center, 122 patients with locally advanced prostatic carcinoma were treated with the LHRH analogue, HOE 766 buserelin from June 1, 1981 to December 31, 1985. The patients were between 54 and 83 years of age (average age, 68.4 years) (Table 1).

Nineteen of the 122 patients received combined treatment with buserelin and androcur for the first 3 months (300 mg androcur i.m. once every two weeks). The remaining 103 patients were treated with buserelin only. According to cytological classification, 16 patients had grade I carcinoma; 64 had grade II carcinoma; and 23 had grade III carcinoma (Table 2).

**TABLE 1.** *Survey of 122 patients with adenocarcinoma of the prostate prior to buserelin therapy*

| | |
|---|---|
| Buserelin | n = 103 |
| Buserelin + Androcur | n = 19 |

n, number of patients.
Data from June 1981–December 1985.

According to TNM classification, 88 (85.4%) of the 103 patients under primary buserelin treatment were in stage T3 NX M0, 15 (14.6%) were in stage T3/T4 NX M1 (Table 3). Patients who had previously undergone treatment such as orchiectomy, adrenalectomy, or estrogen therapy, or who had other malignant tumors, were excluded from this study. Until July 1984, patients with stage D1 and D2 carcinoma were also excluded.

Initial diagnosis was based on the following parameters: case history, physical examination, rectal palpation, electrocardiogram, chest film, intravenous pyelography, sonography, bone scan and CT, acid phosphatase, testosterone, FSH, LH, and prolactin levels, hematological and clinicochemical tests, and, in addition to routine blood tests, serum thyroxine, T3/T4 and cortisol levels (Table 5). Follow-ups were done weekly during the first 2 weeks of therapy, monthly for 3 months thereafter, and every 3 months during the subsequent therapy.

The therapeutic result was evaluated according to NPCP criteria, on the basis of changes in tumor size (rectal palpation), osteoplastic and/or osteolytic bone changes (bone scan), changes in acid phosphatase (RIA), obstruction signs (intravenous urography), grade of cytological regression (aspiration biopsy), and reduction of organic metastases (CT).

Until July 1983, buserelin was given subcutaneously during the initial stage of therapy, with subsequent long-term intranasal application. After that date, subcutaneous injection was abandoned completely at our clinic in favor of intranasal application. From the first through the 28th day of therapy, three daily intranasal doses of 400 $\mu$g buserelin each were given, and, on the 29th day, intranasal application was continued with three daily doses of 300 $\mu$g buserelin each (maintenance dose) (Table 4).

**TABLE 2.** *Morphological grading of malignity for 103 patients with prostatic carcinoma prior to buserelin therapy*

| Grade of malignancy | n | |
|---|---|---|
| I | 16 | 103 |
| II | 64 | |
| III | 23 | |

n, number of patients.
Data from June 1981–December 1985.

**TABLE 3.** *Clinical stage of 103 patients with prostatic carcinoma prior to buserelin therapy*

| Stage | n |
|---|---|
| $T_3$, $N_x$, $M_0$ | n = 88 (85.4%) |
| $T_3/T_4$, $N_x$, $M_1$ | n = 15 (14.6%) |

n, number of patients.
Data from June 1981–December 1985.

## HORMONE STUDIES

During the first 2 weeks of therapy, blood samples were taken twice daily (8 a.m. and 4 p.m.), and, thereafter, once weekly (8 a.m.), to determine testosterone, LH, prolactin, and FSH levels in the serum by means of radioimmunoassay (RIA). Routine blood tests were made to include the determination of thyroxine and triiodothyronine levels in the serum. Cortisol tests were done every 4 weeks. Standard serum testosterone levels as established by radioimmunoassay ranged between 2.5 and 10 ng/dl in adult men. Testosterone levels in a control group of 40 men aged 60–80 years, with prostatic carcinoma, who had undergone surgical castration, ranged between 0.1 and 0.8 ng/dl (average 0.28 ng/dl).

## RESULTS

Prior to long-term treatment, the levels of testosterone and the gonadotrophic hormones, LH and FSH, in the serum were within standard range in all 122 patients. After long-term treatment with buserelin, the serum testosterone and serum LH levels in all patients were found to be within the range seen in castrated men (Fig. 1). Table 5 shows the follow-ups that were done every 4 weeks, or 3 months and 6 months, respectively.

## CYTOLOGY

The rating of tumor response to buserelin therapy was based on the grade of cytological regression found

**TABLE 4.** *Initial dose schedule for buserelin therapy of prostatic carcinoma*

| Dosage (3 daily) |
|---|
| 400 mcg/i.n./day 1–28 → 300 mcg/day/i.n. |

Data from July 1983.

**TABLE 5.** *Clinical follow-ups*

| Every 4 weeks | Every 3 months | Every 6 months |
|---|---|---|
| Blood chemistry | Bone scan | IVP |
| Rectal palpation | Rectal ultrasound | Cat scan |
| Physical status | Chest film | |

Examination included aspiration biopsy and DNA cytophotometry.

on fine-needle aspiration biopsy and on the changes in the DNA content of tumor-cell nuclei measured by DNA single cell-scanning cytophotometry. As the patients were in stage C, and had neither bone metastases nor clinical symptoms, this was the only parameter which would permit an objective evaluation of the effect of buserelin on the primary tumor.

With respect to the regression grade of the primary tumor, the findings on occasional punch biopsies fully corresponded with those of aspiration biopsy. *The cytological regression grading defines the grade of regression in the primary tumor induced by any form of therapy.*

The most important signs of regression are found in the cell nucleus (pyknosis, reduction in size) and in the nucleoli (reduction in size and number) (7). The cytological criteria for regression correspond to those defined for the regression grading by histological methods (7). The cytological regression grading adopted by the Uro-Pathological Group in West Germany distinguishes six grades (Table 7).

Regression grades II–VI indicate good to sufficient therapy response of the tumor as demonstrated by the typical cytological changes. These regression grades do not require any change of treatment. Regression grades VIII and X indicate poor or lacking therapy response of the tumor. Based on our experience with 498 cases under six different forms of therapy, we can state that regression grades VIII or X signal that tumor progression (metastasis) is likely to occur within a few months if therapy is not changed. The difference between good (grades II–VI) and poor regression (grade VIII or X) is statistically significant (7).

The three cases described below show 3 different responses to buserelin therapy and the pertaining characteristic cytological changes.

**Case 1**

M.E., 69 years of age, presented with prostatic carcinoma, stage T3. Prior to therapy, Fig. 2a reveals moderate nuclear polymorphism, pronounced nuclear hypochromatism, and prominent nucleoli: Grade I carcinoma. After 1.5 years of buserelin therapy, Fig. 2b shows reductions in nuclear size, nuclear rarefaction, diminution of nucleoli, pyknotic nuclei, fine vacuolation of cytoplasm and nuclear chromatin. Overall, this is considered good therapy response, corresponding to regression grade II.

**Case 2**

G.P., 69 years of age, presented with prostatic carcinoma, stage T3. Findings prior to therapy, as shown in Fig. 3a, consisted of marked nuclear polymorphism and hypochromatism, disturbance of nuclear arrangement, and prominent nucleoli displaying loss of circularity; some nuclei contain several nucleoli: Grade II carcinoma. After 2.5 years of buserelin therapy, Fig.

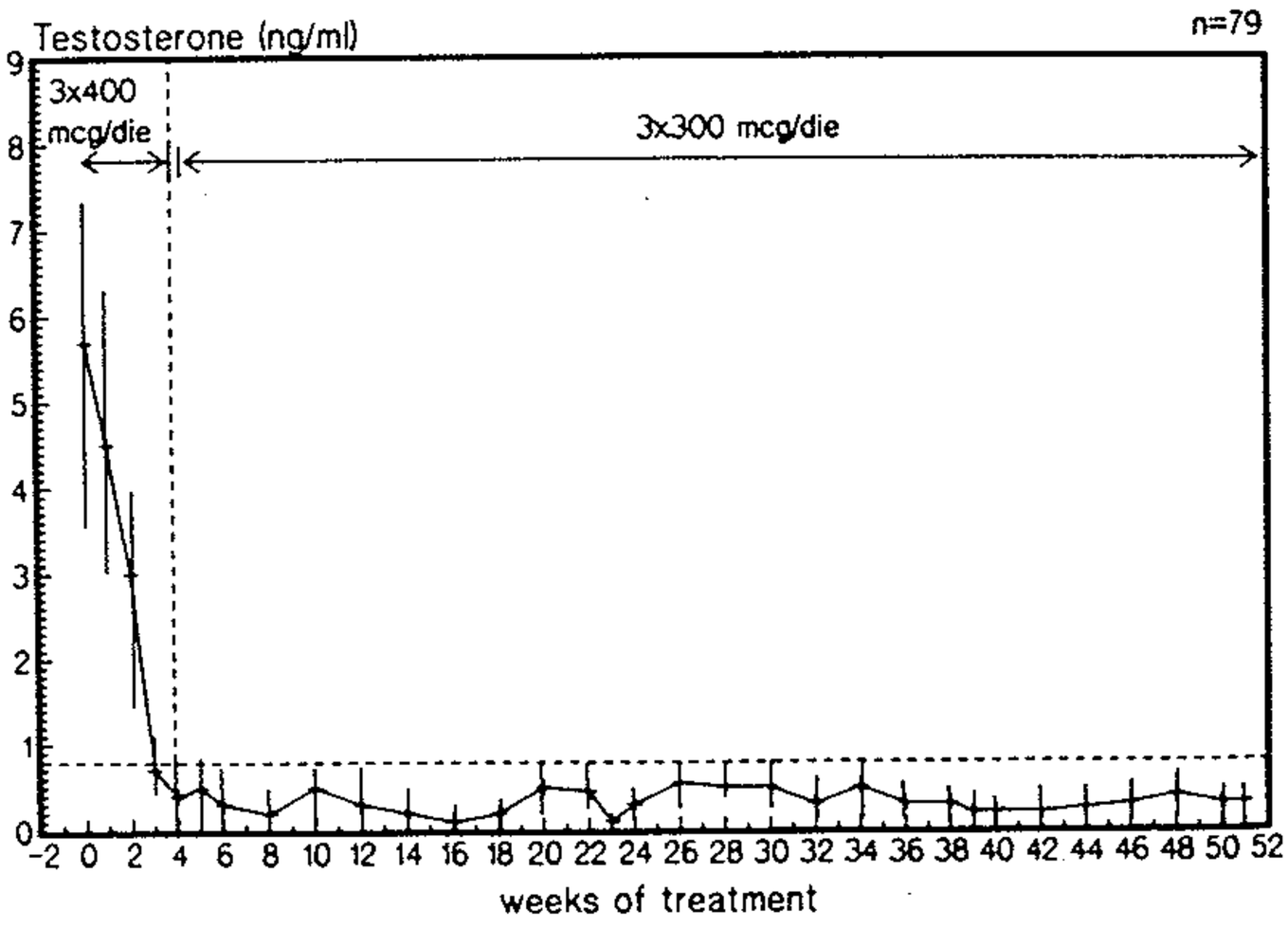


**FIG. 1.** Standard deviation of serum testosterone in 79 patients under buserelin therapy over 52 weeks.

**TABLE 6.** *Period of buserelin therapy of 103 patients with prostatic carcinoma*

| Months | n |
|---|---|
| 12–54 | n = 76 |
| <12 | n = 27 |

n, number of patients.
Data from June 1981–December 1985.

3b shows reductions in nuclear size, localized pyknotic nuclei, and scarcely distinguishable nucleoli: Regression grade IV.

### Case 3

R.E., 75 years of age, had prostatic carcinoma, stage T3. Prior to therapy, Fig. 4a reveals markedly polymorphic and hyperchromatic nuclei, disturbance of nuclear arrangement, prominent nucleoli displaying loss of circularity, and conspicuously dissociated nuclei: Grade III carcinoma. After 6 months of buserelin therapy Fig. 4b demonstrates that the nuclei are still hyperchromatic and polymorphic, with prominent nucleoli; there are rare and only localized regressive changes. Regression grade X therefore indicated a cross-over to secondary therapy with estracyt. After 1.5 years of estracyt therapy, Fig. 4c shows nuclear rarefaction and reduction in size, localized cytoplasmic vacuolation, and nucleoli reduced in size. This is sufficient therapy response: Regression grade VI.

## DNA SINGLE CELL-SCANNING CYTOPHOTOMETRY

While cytology provides the morphological results and thus permits *qualitative rating* of the therapy effect, the analysis of tumor-cell nuclei by DNA single cell-scanning cytophotometry permits *quantitative grading* of regression in the primary tumor. Both methods, particularly DNA cytophotometry, can contribute greatly to a better understanding of biological tumor activity.

It has been known for years that the tumor cell populations, corresponding to a change in the number of chromosomes towards aneuploidy, show a higher DNA content than normal tissues. This finding has been variously confirmed by investigations of different organs, particularly the mammae, lungs, and urinary bladder. It also applies to prostatic carcinoma whose DNA content differs substantially from that of adenoma, which fact assigns DNA cytophotometry its place in the treatment and therapy control of prostatic cancer (15).

As far as we know, the first sequential studies to assess the response of nuclear DNA in prostatic carcinoma to various therapeutic measures have been made at our clinic (7). We found that a statistically significant drop of the grade of ploidy from aneuploid towards diploid occurs in prostatic carcinoma when therapy is successful. If an aneuploidy remains unchanged during therapy, a negative clinical course of the disease may be predicted. Furthermore, we have been able to show that therapy-resistant carcinomas of the prostate differ significantly in their nuclear DNA content from carcinomas with positive therapy responses.

### Methods

The cytophotograms establish the deviation of malignant nuclei from the diploid (2c) set of chromosomes of normal cells. This means that for each patient, the DNA content of normal leukocytes (standard = 2c) has to be measured first and then compared to that of the tumorous nuclei. The values obtained by this comparison are given on the abscissa, in so-called arbitrary units (AU), and the exact number (n) of nuclei measured each time appears on the ordinate (Figs. 5–7). Accordingly, 2c means diploid. 4c tetraploid, and 8c octaploid.

### Results of DNA Cytophotometry

The prognostic value of DNA cytophotograms for buserelin therapy is the same as for any other therapy; it is statistically significant and can be reproduced in the sample at any time. Figures 5–7 show the cytophotograms of the three patients with different therapy responses.

Figure 5 pertains to case 1, patient M.E., with prostatic carcinoma, grade I. Prior to therapy, the frequency peak of DNA distribution was between 4c and 6c, with

**TABLE 7.** *Regression grading according to the Uro-Pathological Group in West Germany*

| Grade of regression | Effect of therapy | Cytomorphological criteria |
|---|---|---|
| 0 | Very good | No carcinoma, marked regressive changes |
| II | Good | Epithelial atypias, carcinoma? Marked regressive changes |
| IV | Satisfactory | Few little carcinoma cell clusters ("residual carcinoma") Marked regressive changes |
| VI | Sufficient | Carcinoma with marked regressive changes |
| VIII | Poor | Carcinoma with poor regressive changes |
| X | None | Carcinoma without regressive changes |

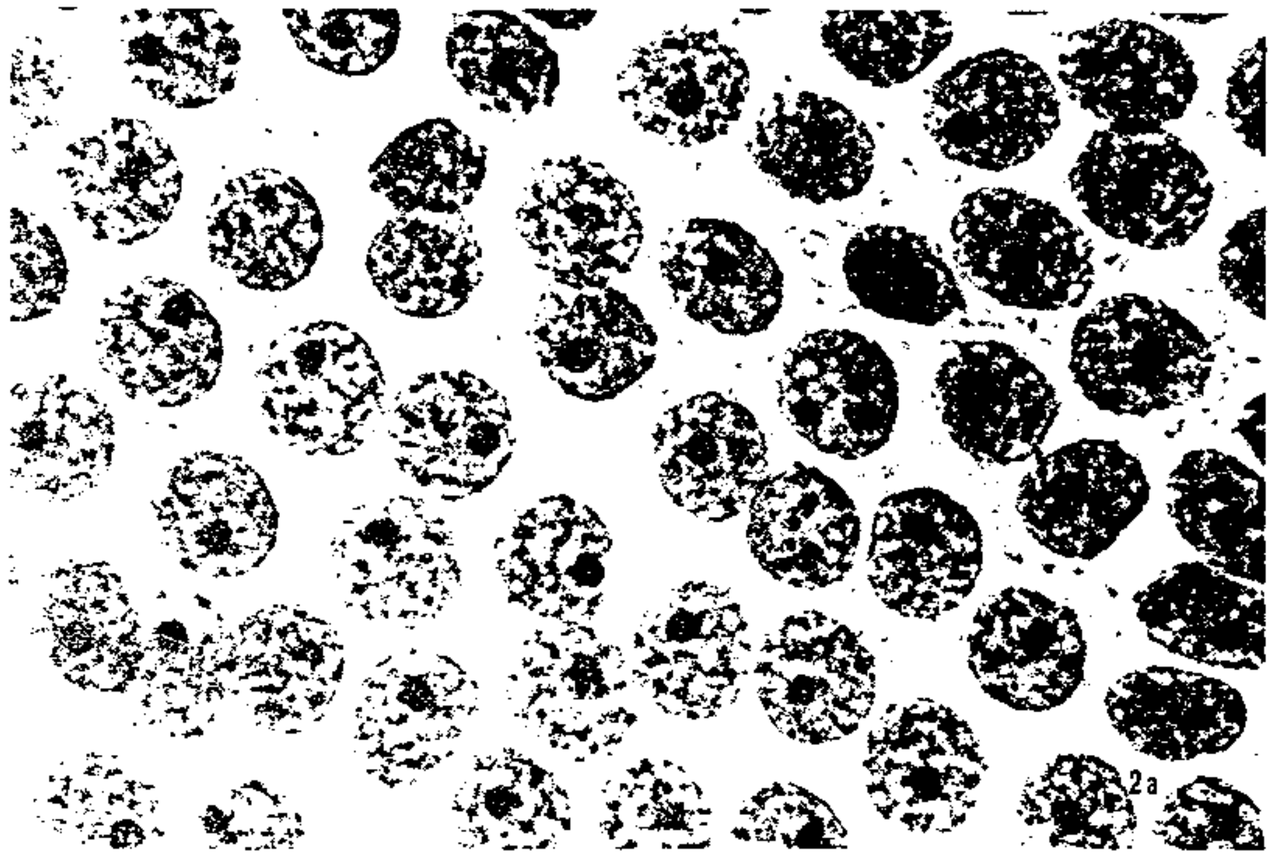

FIG. 2A. Primary cytological finding for patient M.E. prior to buserelin therapy. Cytological smear obtained by aspiration, stained according to Papanicolaou (3,780×).

some values spreading to 8c. Although there is a slight shift of the DNA frequency peak to the left (4c) after 6 months of buserelin therapy, values still spread broadly beyond 4c. However, after 1.5 years of buserelin therapy, the distribution peak is in the diploid range, with sparse spreading up to 4c, indicating a good response to therapy. The histograms verify the morphological and clinical results.

Figure 6 pertains to case 2, patient G.P., with prostatic carcinoma, grade II. Prior to therapy, there is a broad DNA frequency peak between 8c and 10c, with some values spreading to 12c. After 2.5 years of buserelin therapy, there is a slim peak in the diploid (2c) range. The histograms correspond with the morphological findings and the clinically stable condition of the patient after 5 years of therapy.

Figure 7 pertains to case 3, patient R.E., with prostatic carcinoma, grade III. Prior to therapy, the DNA frequency peak reads between 4c and 8c, with some values spreading to 12c. After 3 months of buserelin therapy, the DNA frequency peak was still between 6c and 8c. However, after 1.5 years of estracyt therapy, there is a significant frequency peak in the diploid range. This result corresponds with the morphological findings and the clinically stable condition of the patient.

## RESULTS

We regard a combination of the two methods, i.e., the determination of the grade of cytological regression in the primary tumor together with DNA cytophotometry, as the only reliable and objective procedure to evaluate therapy effect in locally advanced prostatic carcinoma without distant metastases. The classifica-

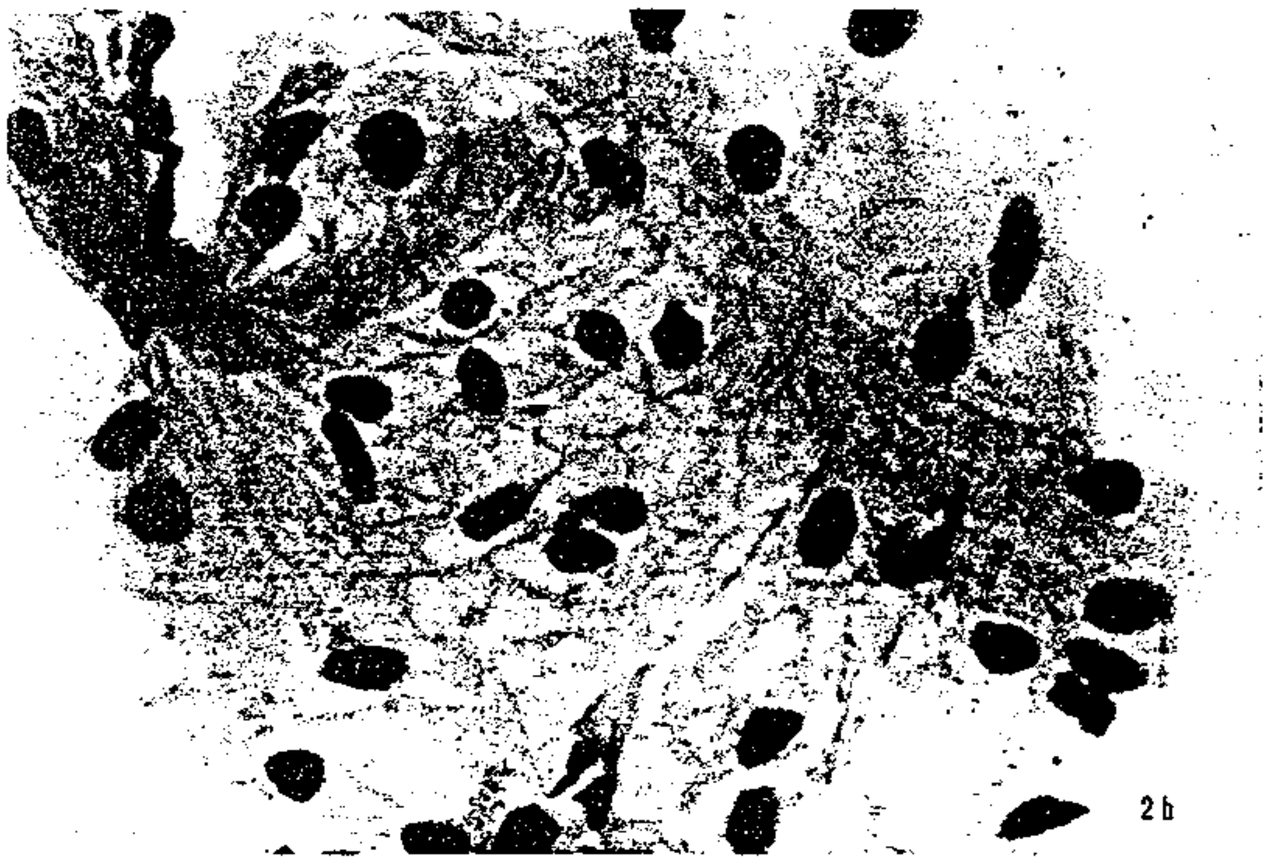

FIG. 2B. Same patient, after 1.5 years of buserelin therapy. Stained according to Papanicolaou (3,780×).

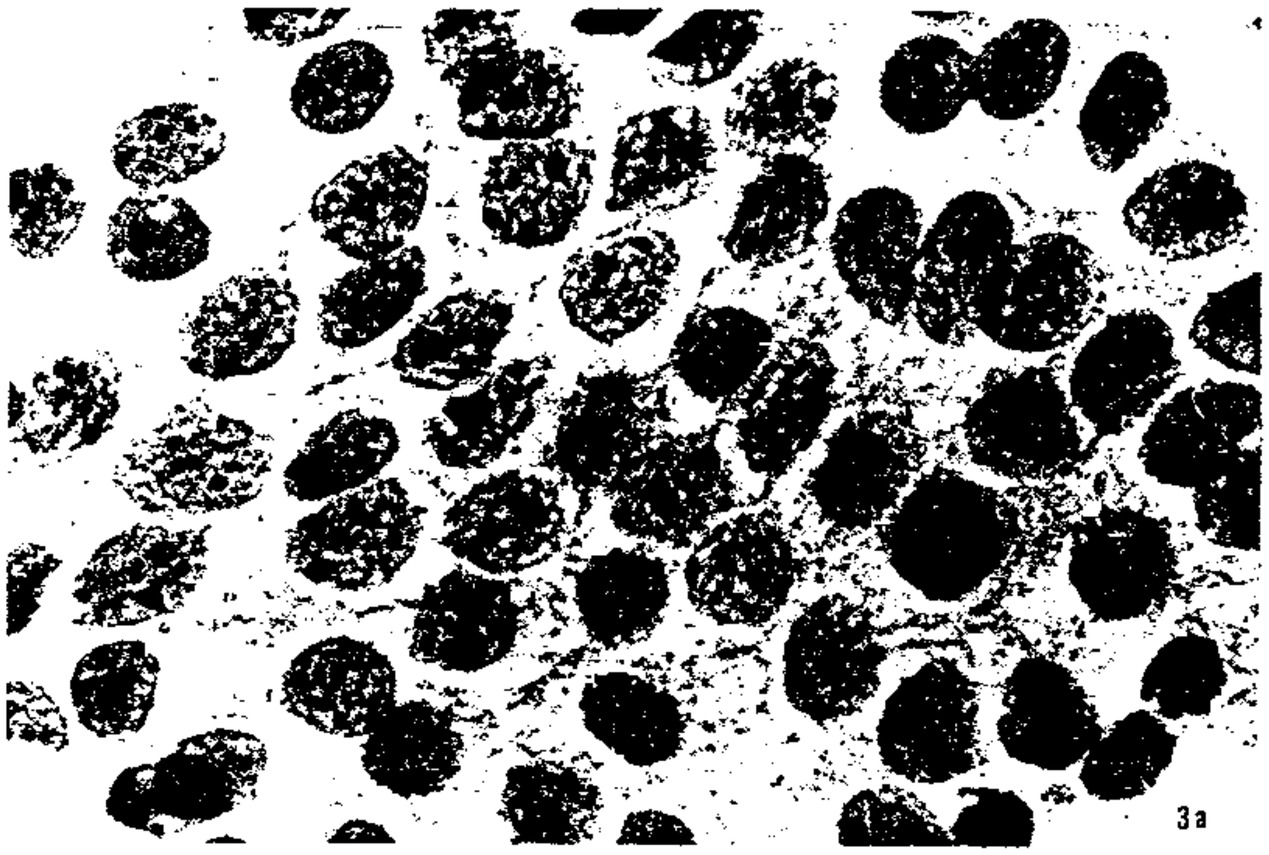


**FIG. 3A.** Primary cytological finding for patient G.P. prior to buserelin therapy. Cytological smear obtained by aspiration, stained according to Papanicolaou (3,780×).

tion of the Uro-Pathological Group "Prostatic Carcinoma" in West Germany was used to assess the regression grade in prostatic cytology (Table 7).

Seventy-six of the 103 patients undergoing exclusive buserelin therapy from June 1981 to December 1985 were treated for periods of 12–54 months, whereas 27 patients were treated for less than 12 months. The average observation period was 28 months (Table 6). According to TNM classification, 68 of the 76 patients were in stage T3 NX M0; 8 patients were in stage T3/T4 NX M1.

Fifty-eight (76.3%) of the 76 patients treated for 12 to 54 months, showed good to satisfactory regression grades in the tumor, while 18 (23.7%) showed poor regression or none, established by both cytology and DNA cytophotometry. In 55 of the 58 patients with favorable regression grades, the clinical findings verified these results; there was no tumor progression (Table 8). Only three of the 58 patients showed local tumor progression (two cases) or beginning bone metastases (one case) despite favorable cytological regression grade.

These three patients, as well as the 18 patients with poor regression or none in the primary tumor, received secondary therapy with estramustin phosphate or, when this therapy failed, tertiary therapy with cyclophosphamide. Six of the 58 patients with good to satisfactory regression grades died from accompanying cardiovascular or cerebrovascular illnesses after 12, 16, 21, 25, or 36 months, respectively.

Thirteen of the 18 patients with poor or no regression were in stage T3 NX M0; five of them were in stage T3/T4 NX M1. The latter died despite change of therapy from cancerous cachexia (after 12, 12, 14, 16, or

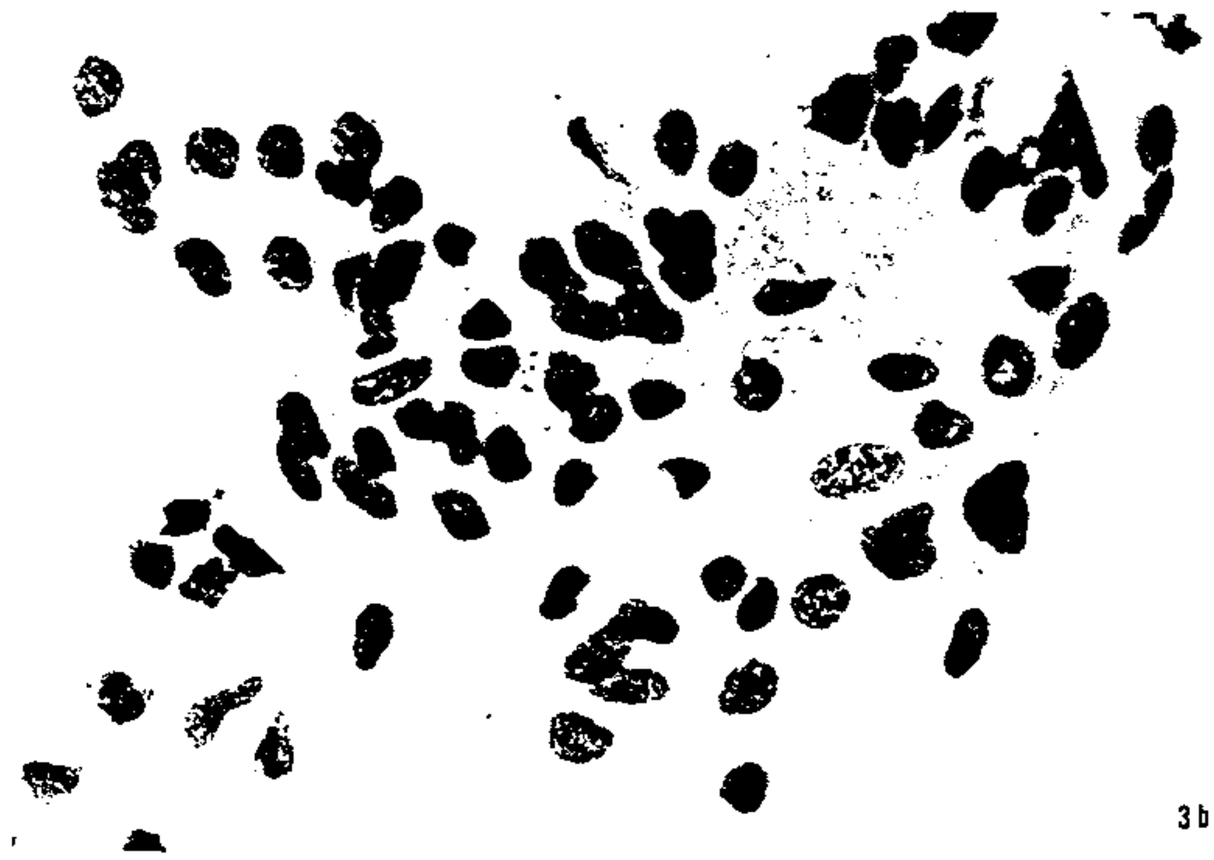


**FIG. 3B.** Same patient, after 1.5 years of buserelin therapy. Stained according to Papanicolaou (3,780×).

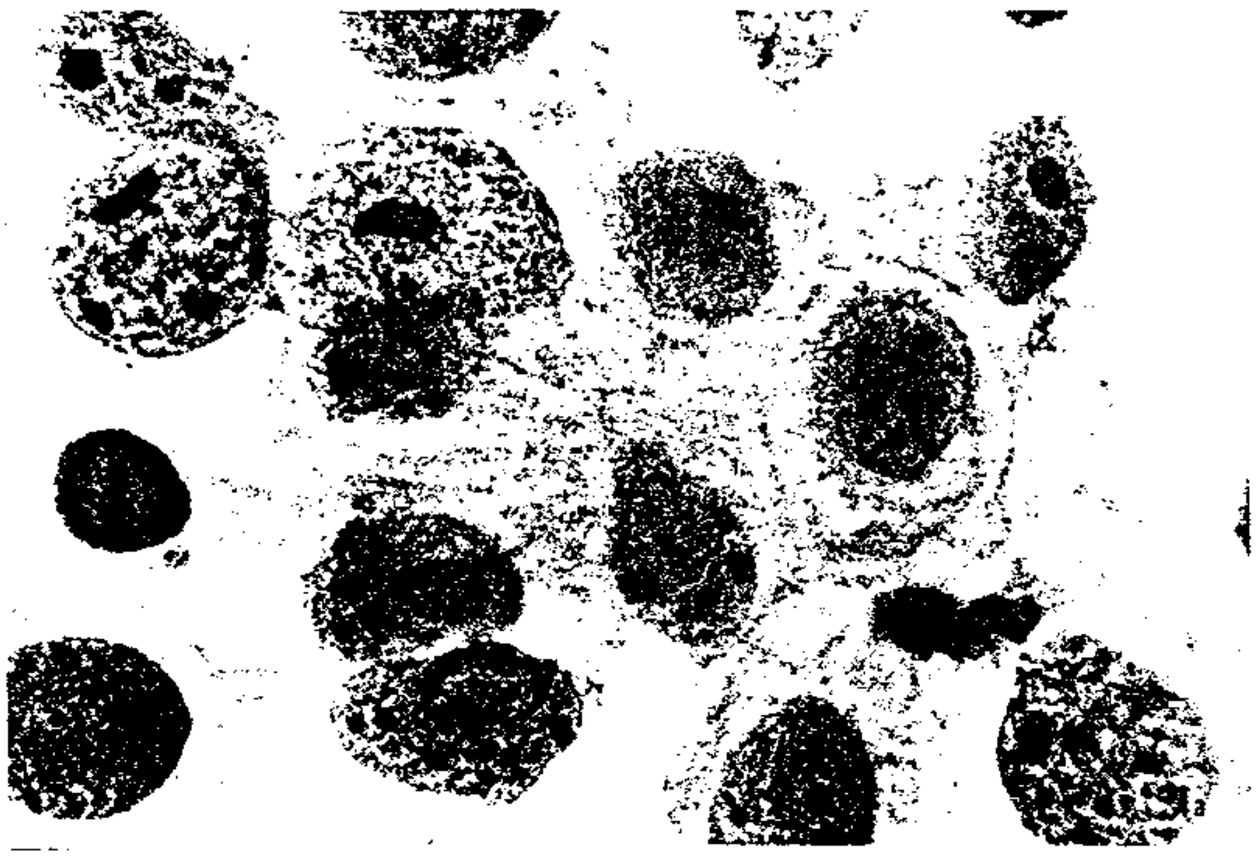

**FIG. 4A.** Primary cytological finding for patient R.E. prior to buserelin therapy. Cytological smear obtained by aspiration, stained according to Papanicolaou (3,780×).

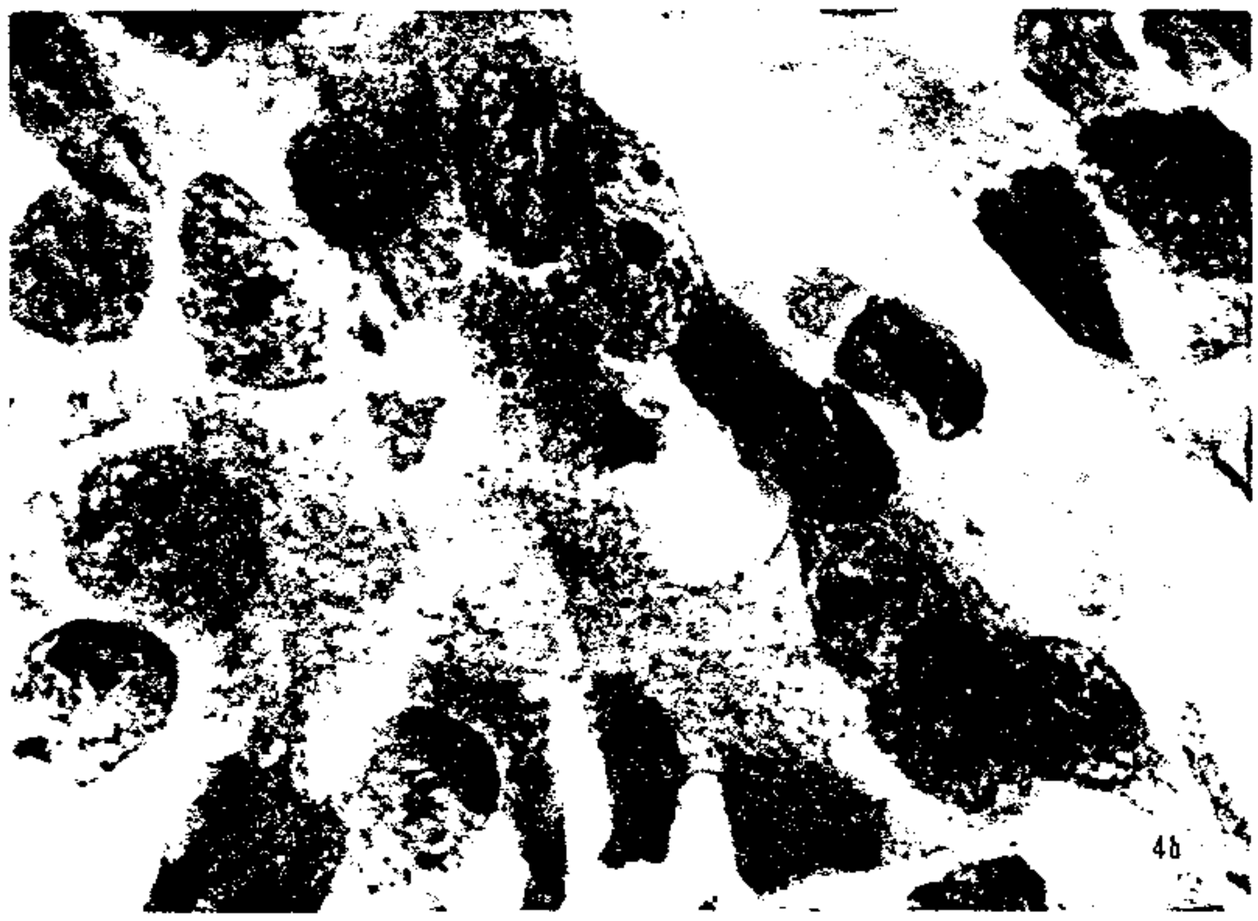


**FIG. 4B.** Same patient, after 6 months of buserelin therapy. Stained according to Papanicolaou (3,780×).

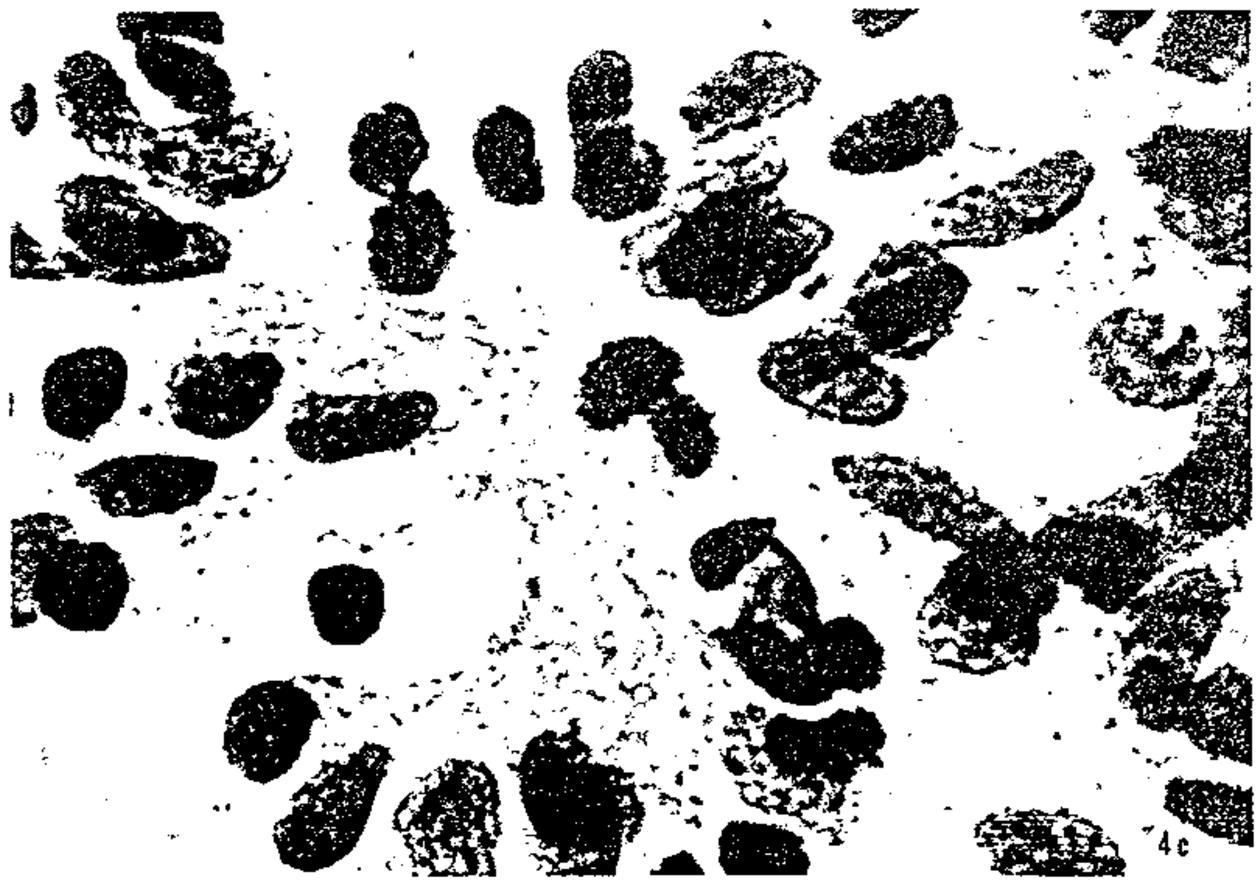


**FIG. 4C.** Same patient, after 1.5 years of secondary estracyt therapy. Stained according to Papanicolaou (3,780×).

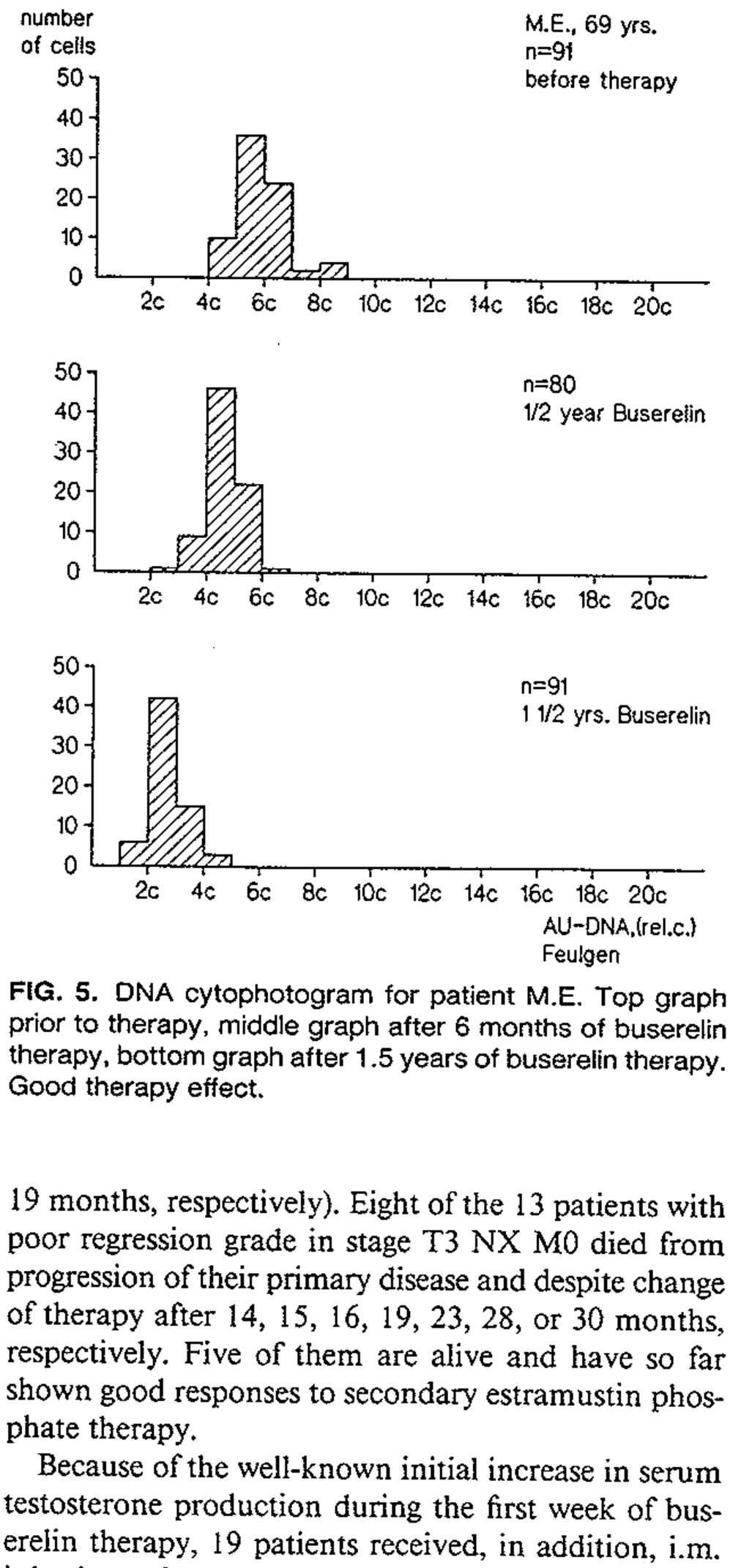


**FIG. 5.** DNA cytophotogram for patient M.E. Top graph prior to therapy, middle graph after 6 months of buserelin therapy, bottom graph after 1.5 years of buserelin therapy. Good therapy effect.

19 months, respectively). Eight of the 13 patients with poor regression grade in stage T3 NX M0 died from progression of their primary disease and despite change of therapy after 14, 15, 16, 19, 23, 28, or 30 months, respectively. Five of them are alive and have so far shown good responses to secondary estramustin phosphate therapy.

Because of the well-known initial increase in serum testosterone production during the first week of buserelin therapy, 19 patients received, in addition, i.m. injections of 300 mg androcur once every 2 weeks over 3 months. This combined therapy prevented the increase in serum testosterone production (Fig. 8). Additional androcur administration will produce this effect only if applied from the very beginning of treatment with buserelin, though. It is expected that androcur administration in the first month of therapy will prove to be sufficient.

Major side effects of buserelin therapy that we have observed in addition to the expected impotence were hot flushes and sweats in 75% of our patients; these usually subsided or disappeared in the course of therapy. In no case was it necessary to discontinue therapy because of such side effects. Patients' compliance was good; however, the patients had been selected accordingly, i.e., cerebrosklerotic or otherwise possibly unreliable patients had not been included in this study.

## DISCUSSION

The questions if and how locally advanced prostatic carcinoma in the non-symptomatic stage, with or without metastases, should be treated is still open to controversy. It would be outside the parameters of this study to attempt an answer here.

One application of hormone withdrawal to treat advanced prostatic carcinoma is to suppress endocrine production with the potent LHRH analogue buserelin. Adequate dosage allows the serum testosterone level to be reliably kept within castrate range for years (2,3,11). In contrast to estrogen therapy, buserelin therapy does not entail cardiovascular complications. It also offers the advantage of avoiding the psychical stress of orchiectomy.

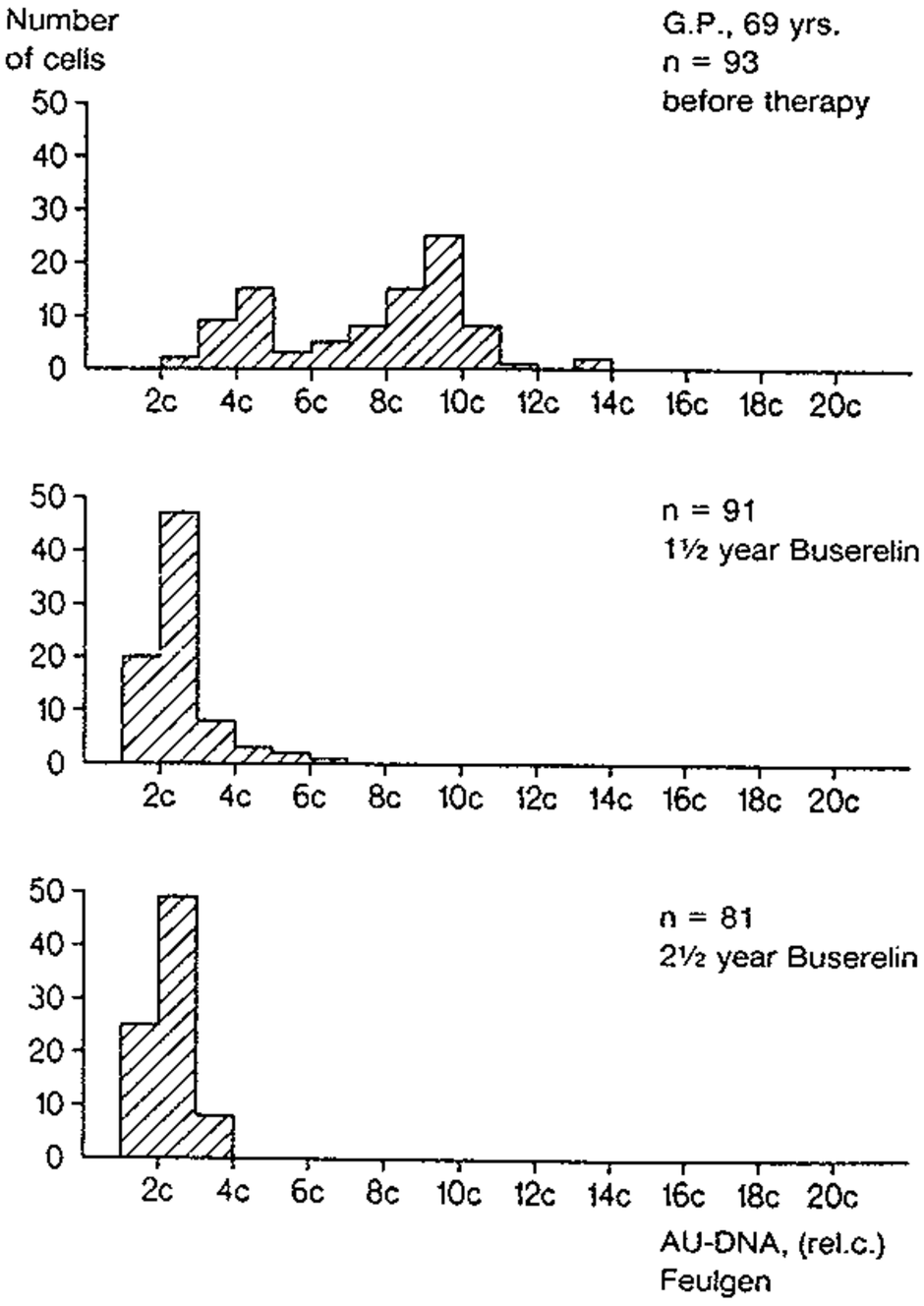


**FIG. 6.** DNA cytophotogram for patient G.P. Top graph prior to therapy, middle graph after 1.5 years of buserelin therapy, bottom graph after 2.5 years of buserelin therapy. Good therapy effect.

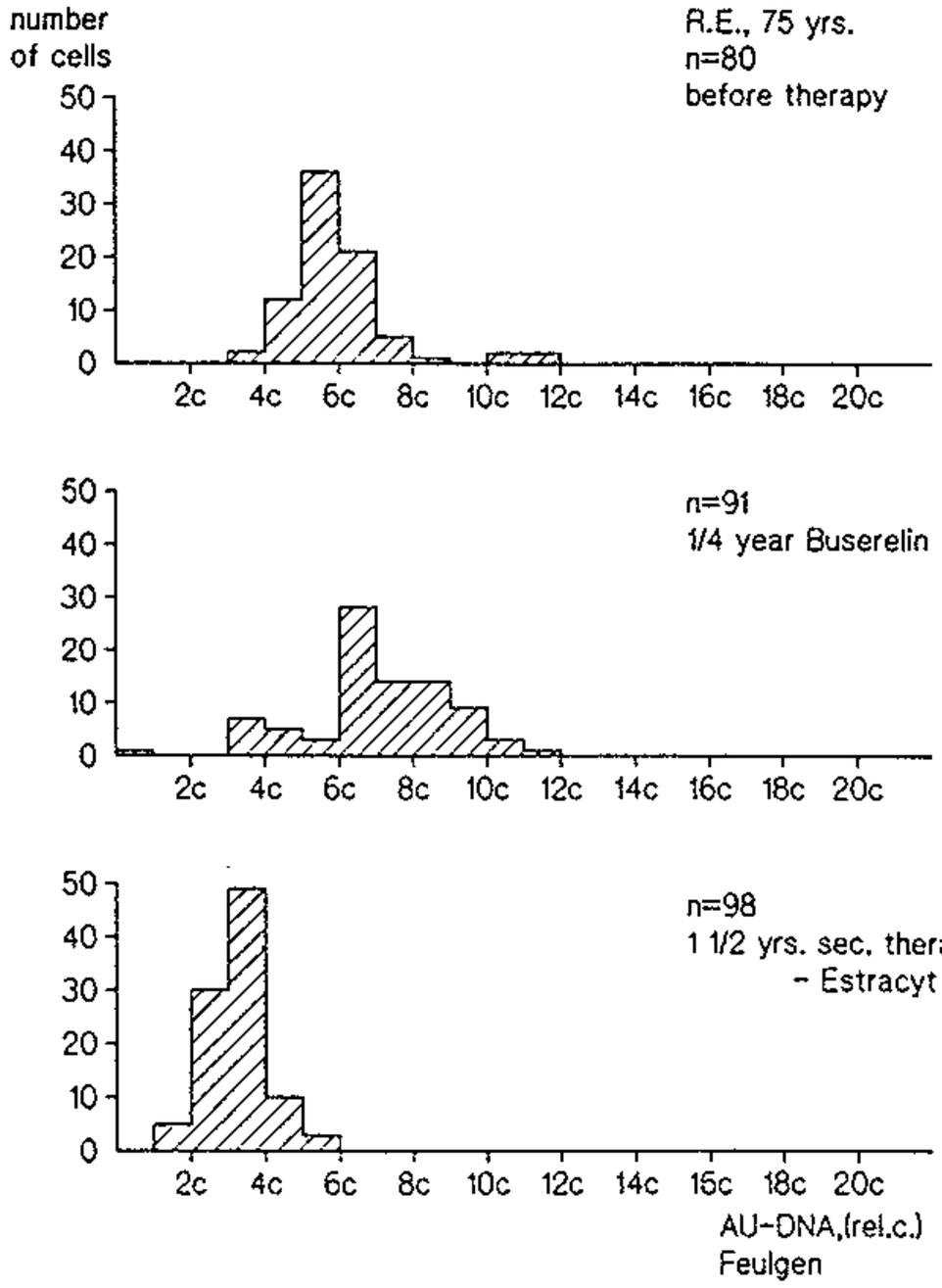


**FIG. 7.** DNA cytophotogram for patient R.E. Top graph prior to therapy, middle graph after 3 months of buserelin therapy; unsatisfactory therapy effect. Bottom graph after 1.5 years of secondary estracyt therapy; satisfactory therapy effect.

76.3% of the 76 patients with prostatic carcinoma, stage T3 NX M0, who were treated with buserelin for periods of 12–54 months, showed good to satisfactory regression grades which corresponded to clinical findings, while 23.7% showed poor regression or none. Therapy for the latter group was changed to estramustin phosphate or cyclophosphamide. Only in three cases did the results of aspiration biopsy differ from the clinical course of the disease. In these three cases, local tumor progression or bone metastases requiring a change of therapy occurred despite favorable regression grade. This discrepancy between cytological and DNA–cytophotometrical findings and the clinical course of the disease is probably due to the fact that only hormone-sensitive tumor tissue was aspired in biopsy.

On the basis of our experience with aspiration biopsy (more than 10,000 aspiration biopsies in the prostate), we maintain that the assessment of therapy effect on locally advanced prostatic carcinoma without distant metastases can be objectively judged solely by the

**TABLE 8.** *Results of cytology and DNA cytophotometry for 76 patients under buserelin therapy*[a]

| Grade of regression | n |
|---|---|
| II–VI | n = 58 (76.3%) |
| VIII–X | n = 18 (23.7%) |

n, number of patients.
[a] Treatment from 12–54 months.

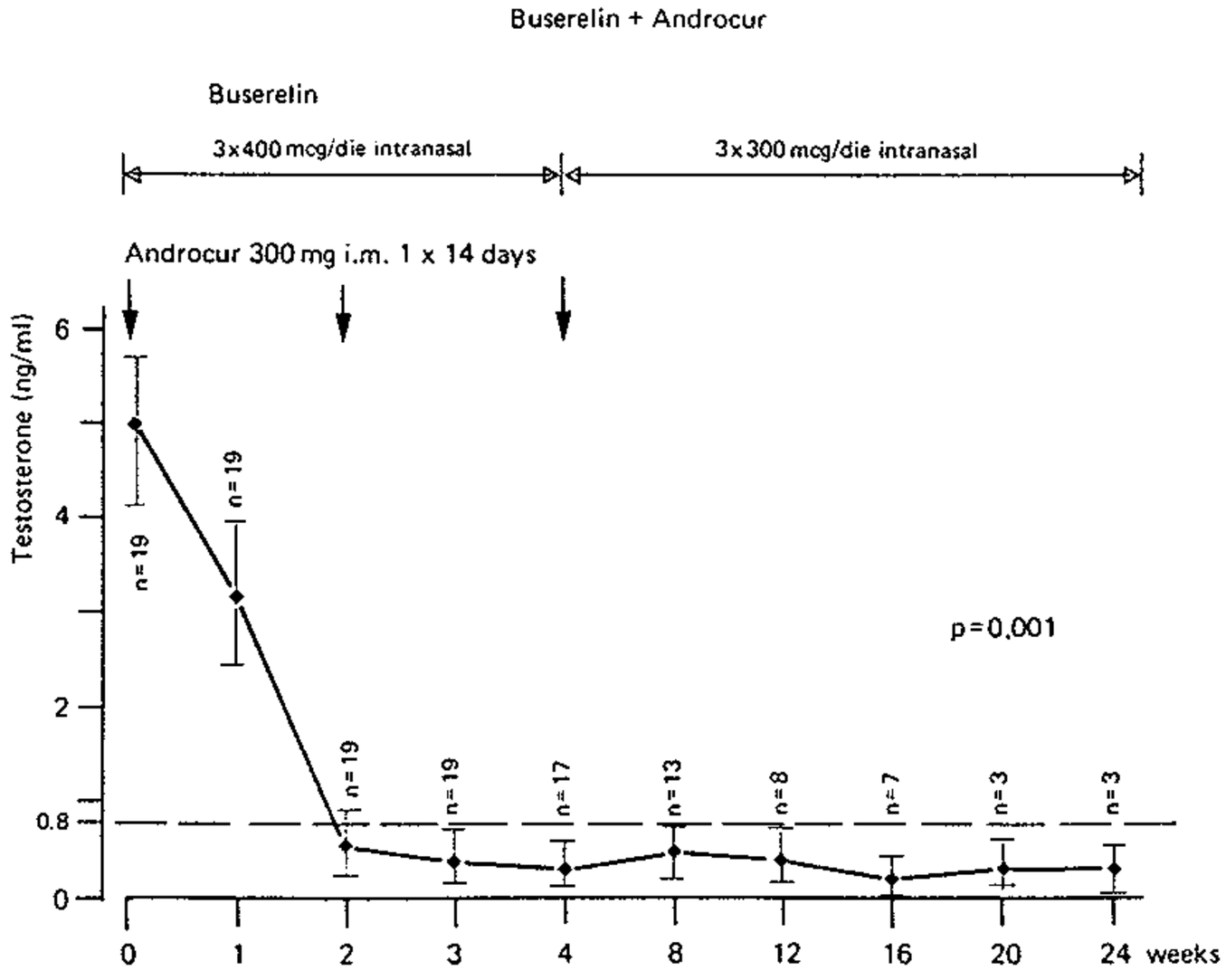


**FIG. 8.** Standard deviation of serum testosterone in 19 patients under combined buserelin/androcur therapy over 24 weeks.

changes in the primary tumor itself, regardless of the form of therapy chosen (estrogen, antiandrogens, orchiectomy, irradiation).

While cytology gives morphological, i.e., qualitative, information about tumor response to therapy, DNA single cell-scanning cytophotometry permits a quantitative assessment of the changes in the ploidy grades present in the primary tumor. Our cytological and clinical experience has proven that patients with poor regression are likely to develop distant metastases or local tumor progression within a few months if therapy is not changed.

Especially for follow-ups, we therefore consider aspiration biopsy of the prostate with cytological regression grading and DNA single cell-scanning cytophotometry indispensable. The necessity of suppressing androgen production in the suprarenal gland is still open to question. Labrie et al. strongly postulate—although on the basis of rather questionable results—that only the complete suppression of suprarenal androgen production will bring the decisive breakthrough in the treatment of prostatic carcinoma (4,6).

In summary, it can be stated on the basis of our studies that the treatment with buserelin induces a positive therapy response in the primary tumor in more than 75% of primary, locally advanced, and inoperable prostatic carcinoma. The clinical castration effect produced by buserelin through selective suppression of the gonadotrophic secretion of the pituitary gland is—as implied by the term—no more effective than surgical castration, which also halts the production of testicular testosterone only. The suppression of gonadotrophic hormones induced by buserelin, however, is reversible and spares patients the psychic stress of orchiectomy. This appears to be utterly important in light of the fact that in 20–40% of patients with locally advanced primary prostatic carcinoma, the primary tumor is hormone-refractory and surgical castration would prove unnecessary after all.

In contrast to estrogen therapy, buserelin therapy is free of major side effects, apart from the androgen deficiency syndrome (hot flushes, sweats, impotence). Finally, the development of depot forms of LHRH analogues will resolve the question of compliance. ₡

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