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PRELIMINARY RESULTS OF A PROSPECTIVE RANDOMIZED STUDY COMPARING RADICAL PROSTATECTOMY VERSUS RADICAL PROSTATECTOMY ASSOCIATED WITH NEOADJUVANT HORMONAL COMBINATION THERAPY IN T₂₋₃ N₀ M₀ PROSTATIC CARCINOMA

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ABSTRACT

Objectives. To evaluate the short- and long-term effects of neoadjuvant hormonal treatment in locally confined prostate cancer.

Methods. We report the preliminary results of 354 patients (199 with a clinical T2 tumor and 155 with a clinical T3 tumor) of whom 164 randomly received neoadjuvant total androgen deprivation using a luteinizing-hormone-releasing hormone (LHRH) analog (goserelin) plus flutamide for a period of 3 months.

Results. Serum prostate-specific antigen (PSA) levels and prostatic volume decreased from a mean of 19.9 ng/mL and 37.7 cm³ to a mean of 0.8 ng/mL and 26.5 cm³ after 3 months of neoadjuvant therapy. "Clinical downstaging" was seen in 32% in the neoadjuvantly treated group. "Pathological downstaging" percentages were 6% and 16% in the direct radical prostatectomy group and neoadjuvantly-treated group, respectively ($P < 0.01$). In patients with clinical T2 tumors, a significant difference in number of positive margins was shown in favor of the neoadjuvantly treated group ($P < 0.01$). In patients with clinical T3 tumors, a significant difference could not be detected ($P = 0.14$). In 215 patients with a mean follow-up time of 15 months, the calculated 95% confidence intervals of mean time of PSA progression-free survival were 26 to 35 months in the neoadjuvantly-treated group and 28 to 37 months in the direct radical prostatectomy group, indicating no significant differences between treatment groups. However, follow-up time is currently too short to draw definite conclusions.

Conclusions. These early data confirm high understaging percentages in clinical staging. The clinical relevance of the statistically significant smaller numbers of patients with positive margins in the neoadjuvantly treated group with a clinical T2 tumor will have to be confirmed when further follow-up allows an accurate evaluation of time to PSA progression, local recurrence, and distant metastases. Presently, neoadjuvant therapy is not advisable outside clinical research settings. © 1997 by Elsevier Science Inc. All rights reserved. UROLOGY 49(Suppl 3A): 65-69, 1997.

Clinical staging of localized cancer is hampered by inaccuracy, mainly leading to understaging. Consequently, most series of radical prosta-

tectomies contain a large number of patients with tumors extending beyond the prostate. From this experience it is clear that radical surgery is feasible in this category of patients. Since it is known that a localized lesion can be reduced in size by hormonal treatment, the question as to whether preoperative hormone manipulation enhances surgical curability has remained since 1941 when the androgen-dependency of prostatic carcinoma was first described.¹ With the availability of reversible luteinizing-hormone-releasing hormone (LHRH) analogs and nonsteroidal antiandrogens, interest in preoperative hormonal manipulation has re-

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This article was supported by grants from Schering Plough, Kenilworth, USA, and Zeneca, Macclesfield, Cheshire, England.

For additional members of the European Study Group on Neoadjuvant Treatment of Prostate Cancer, see the Appendix.

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cently been reawakened. Presently, neoadjuvant hormonal manipulation in prostatic carcinoma is not a commonly accepted treatment. The published clinical and pathological studies on this subject are conflicting.² The importance of the question "Is neoadjuvant therapy really beneficial?" has been shown in two conflicting articles published in 1993: Oesterling *et al.*³ concluded that "preoperative androgen deprivation therapy has little or no benefit for decreasing the extent of tumor or pathological stage; the concept of downstaging is misleading"; Fair *et al.*⁴ concluded that "although it is not possible to state currently that any patient has received benefit from neoadjuvant hormonal therapy, it is likewise not possible to be dogmatic in the assertion that neoadjuvant therapy is not beneficial." Therefore, it is important that further clinical studies, preferentially randomized trials, should be performed to determine the real value of preoperative hormonal therapy. We herein report the preliminary results of such a randomized trial.

MATERIALS AND METHODS

In October 1991, we started a randomized, multicenter study to evaluate the short- and long-term effects of neoadjuvant hormonal treatment in prostatic carcinoma. The primary objective of the study was to evaluate the effect of neoadjuvant therapy on time to PSA progression. The secondary objectives were to compare the ease and complications of surgery, the histopathologic grading and staging, and the positivity of lymph nodes and surgical margins between both groups.

Patients with newly diagnosed T2-3N0M0 prostatic carcinoma confirmed by histopathologic analysis were randomized for direct radical retropubic prostatectomy (DP) or neoadjuvant combination therapy (NEO) using the LHRH analog goserelin (3.6 mg subcutaneous depot each month) plus flutamide (250 mg thrice daily) for a period of 3 months followed by radical prostatectomy. At randomization, patients were stratified for clinical T category and pathological grade of the tumor for each participating center. Serial PSA levels, pre- and post-treatment prostate volumes measured by transrectal ultrasound (TRUS), clinical stage before and after neoadjuvant therapy, and ease of surgery were investigated. The pathologic stage of the tumor was assessed by each local pathologist using a standardized prostatectomy step-section protocol. Radical prostatectomy specimens were fixed and radially sectioned in 0.5 cm thick segments from the apex to the base and submitted in their entirety for histopathologic examination. All surgical specimens were classified according to the TNM (tumor, nodes, metastases) classification system.⁵ Using this classification, a pathologic T0 (pT0) tumor was when there was no evidence of the primary tumor; pT1 indicated that the tumor was an incidental histologic finding (only microscopic foci of carcinoma); pT2 indicated that the tumor was present grossly but limited to the gland, while pT3 tumors invaded beyond the prostatic capsule or bladder neck or seminal vesicle; a pT4 tumor invaded adjacent structures other than those listed in T3. The "clinical downstaging" percentages for those who underwent neoadjuvant treatment were assessed. A patient was clinically downstaged if after 3 months of neoadjuvant treatment the clinical stage of the tumor was lower than the clinical stage at baseline. A patient was "path-

ologically downstaged" if the final pathologic stage was lower than the clinical stage at baseline.

The primary endpoint used for the determination of the sample size was an increase of PSA > 1 ng/mL after surgery on two subsequent occasions. The goal was to have 200 evaluable patients in each treatment arm. This estimate was based on the probability of detecting a 15% difference (from 35% in the direct prostatectomy group to 20% in the neoadjuvantly-treated group) in the number of patients that develop a rise in PSA during the study follow-up period of 2 years using a two-sided log rank test with a power of 90% and a type I error rate of 5%.

Statistical analyses were performed using the Mann-Whitney U test and chi-square test for numerical and categorical data, respectively. To compare the time to PSA progression between both treatment arms, 95% confidence intervals (CI) of the mean time of PSA progression-free survival were calculated.

RESULTS

Presently, the preliminary results from 354 patients are available. Stratification for initial stage and grade for these patients was comparable in the two treatment arms. In the NEO-group, serum PSA levels decreased from a mean (SD) of 19.9 (17.5) ng/mL to a mean of 0.8 (2.1) ng/mL after 3 months of neoadjuvant therapy. After 3 months of neoadjuvant therapy, 40% of the patients had undetectable PSA levels and the prostatic volume, as assessed by ultrasound, had decreased from a mean of 38 (19) cm³ to a mean of 26 (15) cm³ (30% decrease). The mean duration of surgery and blood loss were not significantly different ($P = 0.16$ and $P = 0.93$, respectively). The mean hospitalization time was 17 days in the DP group and 16 days in the NEO group ($P = 0.71$). The reported nature, severity, and incidence of complications (17% of the patients in the NEO group; 18% in the DP group) occurring within 30 days postoperatively was not significantly different ($P = 0.83$).

Table I demonstrates the initial clinical stage compared with the final histopathologic stage after surgery for both treatment groups. In the NEO group, "clinical downstaging" was seen in 53 out of 164 patients (32%) after 3 months of neoadjuvant therapy prior to surgery. In the NEO group and the DP group, "pathologic downstaging" was seen in 26 out of 164 patients (16%) and in 11 out of 190 patients (6%), respectively. The difference in pathologic downstaging percentages between both groups was statistically significant ($P < 0.01$). Cancer could not be found in the prostatectomy specimen in 4 of the 164 patients who were treated neoadjuvantly. Initially, we had 6 patients who appeared to be downstaged to pT0. One patient with a clinical T2 tumor, in whom no tumor could be found in the radical prostatectomy specimen after the first pathologic examination using step-sectioning of the entire prostate, was reviewed by the

TABLE I. Final histopathological stage after surgery compared with the initial clinical stage at diagnosis

	pT0N0	pT1N0	pT2N0	pT3N0	pT4N0	pTxN+
Neo T2 (n = 92)	3 (3%)	5 (6%)	53 (58%)	25 (27%)	2 (2%)	4 (4%)
Dir T2 (n = 107)	—	2 (2%)	34 (32%)	51 (47%)	3 (3%)	17 (16%)
Neo T3 (n = 72)	1 (1%)	—	17 (24%)	34 (47%)	3 (4%)	17 (24%)
Dir T3 (n = 83)	—	—	9 (11%)	43 (52%)	4 (5%)	27 (32%)

Dir, Direct prostatectomy group; Neo, neoadjuvant-treated group.

local pathologist. Immunohistochemical examination (prostatic acid phosphatase [PAP] and PSA) revealed a residual focus of carcinoma. In another patient who was downstaged to pT0 according to the local pathologist, another pathologist who used the same slides recognized a small focus of carcinoma. The high understaging percentages are remarkable: 102 out of 190 patients (54%) in the DP group and 51 out of 164 patients (31%) in the NEO group. There were significantly more patients understaged in the DP group ($P < .01$). Lymph-node-positive disease was found in 21 out of 164 patients treated neoadjuvantly and in 44 out of 190 patients in the DP group. This difference in favor of the neoadjuvant group is statistically significant ($P = 0.01$). In the NEO group, the proportions of patients with organ-confined and specimen-confined disease were 45% and 24%, respectively. In the DP group, these percentages were 21% and 25%, respectively, indicating a significant difference in favor of the neoadjuvantly-treated patients ($P < 0.01$). The effect of 3 months neoadjuvant combination therapy on positive margins after prostatectomy is indicated in Table II.

PSA follow-up data for the comparison of the time to PSA progression between both treatment arms were available from 215 patients with a mean follow-up time of 15 months. In the DP group, 25

out of 108 patients (23%) experienced an increase of PSA > 1 ng/mL after surgery on two subsequent occasions. The mean time of PSA progression-free survival in this group was 32.5 months (95% CI: 28.1 to 36.9 months). In the NEO group, 24 out of 107 patients (22%) had an increasing PSA. The mean time of PSA progression-free survival in this group was 30.8 months (95% CI: 26.4 to 35.1 months).

COMMENT

Our results confirm the results described in literature.² After 3 months of neoadjuvant treatment, clinical downstaging in one-third of the patients occurs, but clinical downstaging cannot always be confirmed pathologically. Pathologic downstaging occurred in a significantly larger percentage in the neoadjuvantly-treated group. The clinical relevance of the statistically significant higher numbers of patients with pathologic downstaging after neoadjuvant treatment must be confirmed when further follow-up allows an evaluation on time to PSA progression. Pathologic downstaging can be a consequence of phenotypic changes of tumor cells that makes recognition of them as persisting cancer cells difficult.⁶ The pathologist should be aware of phenotypic changes because the atrophic cells can easily be confused with lymphocytes, resulting

TABLE II. Effect of 3 month neoadjuvant combination therapy on positive margins after radical prostatectomy

	Negative Margins (%)	Positive Margins (%)	No Radical Prostatectomy (N+ disease) (%)
Neo T2 (n = 92)	79 (86%)	13 (14%)	—
Dir T2 (n = 107)	66 (62%)	38 (36%)	3 (2%)
Neo T3 (n = 72)	38 (53%)	31 (43%)	3 (4%)
Dir T3 (n = 83)	31 (37%)	49 (59%)	3 (4%)
Total Neo (n = 164)	117 (71%)	44 (27%)	3 (2%)
Total Dir (n = 190)	97 (51%)	87 (46%)	6 (3%)

Neo, Neoadjuvant group; Dir, direct prostatectomy group.

Comparison of neoadjuvant group versus direct prostatectomy group in patients with a clinical T2 tumor: $P < .01$.

Comparison of neoadjuvant group versus direct prostatectomy group in patients with a clinical T3 tumor: $P = .14$.

Comparison of both cT2 and cT3 neoadjuvant groups versus direct prostatectomy groups: $P < .01$.

in false negative histologic results. Immunostaining of tumor cells and the use of monoclonal antibodies against specific cytokeratins can be very helpful to detect immunohistochemically-persisting tumor cells and positive margins.⁷ These new pathology tools were only occasionally used in our study. For an accurate evaluation of the real value of false-negative histologic results, it would be worthwhile to standardize pathologic review and use immunostaining or monoclonal antibodies against specific cytokeratins throughout the study. Unfortunately, this was not feasible in the present study. Edelstein *et al.*⁸ retrospectively investigated the lymph nodes of 36 patients who underwent a radical prostatectomy. In these patients, clinical follow-up was available using reverse transcriptase polymerase chain reaction (RT-PCR) results, which demonstrated PSA mRNA activity in the lymph nodes of 16 out of 36 (44%) patients. It was remarkable that 14 out of 16 patients developed a rise of PSA, demonstrating that using conventional pathologic examination, it is likely that we miss a percentage of microscopic lymph node metastases. This may also account for the detection of prostatic cancer in surgical margins. Using neoadjuvant treatment it may be even more difficult to identify prostatic cancer cells. The distribution of the tumor grade categories in the NEO group was not significantly different when compared with the DP group. Hence, a statistically significant lower incidence of lymph-node-positive disease in the NEO group fastens suspicion on a false-negative histologic examination rate in the neoadjuvantly-treated group if it turns out that this does not translate into a longer PSA progression-free survival time.

The prostatic volume after 3 months of neoadjuvant treatment decreased from a mean of 37.7 to 26.5 cm³. This important downsizing could result in a decreased number of complications during and after surgery. The literature is contradictory on whether neoadjuvant therapy does or does not complicate the prostatectomy itself. Macfarlane *et al.*⁹ and Soloway *et al.*¹⁰ reported no change in blood loss and operative time, but van Poppel *et al.*¹¹ reported a greater incidence of complications and blood loss. Schulman¹² reported less blood loss and shorter operating time. In our series, significant advantages in favor of the neoadjuvantly-treated group could not be detected when looking at surgery time, blood loss during surgery, hospitalization period, and complication rate. It is noteworthy that the hospitalization time in European countries still largely exceeds the duration of hospital stay in the USA.

When comparing the number of positive margins after prostatectomy in both groups, a signifi-

cant advantage in the NEO group was seen ($P < 0.01$). When looking at the clinical T2 (cT2) group, this advantage is significant ($P < 0.01$). When evaluating the clinical T3 group, a statistically significant advantage in number of positive margins could not be shown ($P = 0.14$). These results are in accordance with the results of a study reported by van Poppel *et al.*¹¹ A significant decrease in the number of patients with positive margins in favor of the NEO group has also been reported by Labrie *et al.*,¹³ Goldenberg *et al.*,¹⁴ and Soloway *et al.*,¹⁰ all of whom investigated the effects of neoadjuvant treatment mainly in patients with clinical organ confined (cT stage ≤ 2) tumors. In our study in patients with a clinical T2 tumor, at least one surgical margin was positive in 14% of the patients who underwent neoadjuvant treatment, compared to 36% of the controls. These results are comparable to the 13% and 38% rates, respectively, obtained by Labrie *et al.*,¹³ but differ from those of a randomized study by Goldenberg *et al.* who, using cyproterone acetate for neoadjuvant treatment, reported a difference of 37% in the rate of positive surgical margins between treated patients (positive margin rate 28%) and untreated controls (positive margin rate 65%).¹⁴ Soloway *et al.* reported positive margins in 18% and 48%, respectively.¹⁰ Oesterling *et al.* found higher rates (86%) of positive margins in patients who had received some type of preoperative androgen deprivation. Most of these patients had stage cT3 cancer, so the implications for patients with apparently less extensive cancers are unclear.³

The mean time of progression-free survival showed no significant differences between treatment groups. However, we must be cautious in drawing conclusions from an analysis that is preliminary because the number of evaluable patients needed in this study is 400. We only have 215 patients at this time for the evaluation of the time of PSA progression-free survival.

Realizing that there is a strong relationship between tumor volume, seminal vesicle invasion, the extent of capsular invasion, and metastases, it is likely that the benefit of neoadjuvant hormonal treatment, if any, lies in a decrease of positive margins in a subgroup of patients with clinical T1-2 tumors, resulting in an enhanced local control and possibly also survival. The benefit of neoadjuvant hormonal treatment in patients with clinical T3 tumors remains controversial. Further follow-up is necessary to provide the still-lacking information on both local effects and survival advantages of neoadjuvant hormonal manipulation in prostatic carcinoma. Presently, neoadjuvant therapy is not advisable outside clinical research settings.

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APPENDIX

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