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NEOADJUVANT THERAPY BEFORE RADICAL PROSTATECTOMY FOR CLINICAL T3/T4 CARCINOMA OF THE PROSTATE: 5-YEAR FOLLOWUP, PHASE II SOUTHWEST ONCOLOGY GROUP STUDY 9109

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ABSTRACT

Purpose: Several investigators have examined the role of hormonal therapy before definitive local therapy for locally advanced prostate cancer to improve outcome. We evaluated the resectability rate and clinical response rate to 16 weeks of total androgen blockage therapy for clinically locally prostate cancer before radical prostatectomy, and progression-free survival in this multiinstitutional study.

Materials and Methods: Southwest Oncology Group 9109 was a phase II feasibility study designed to treat patients with clinical stage C prostate cancer (T3, T4, N0 and M0). Cases were classified by stage T3 versus T4 and bulky (greater than 4 cm.) versus nonbulky (or less 4 cm.) disease. The neoadjuvant agents used were goserelin and flutamide before radical prostatectomy.

Results: A total of 62 patients were accrued to the study and 1 patient was ineligible. There were 2 protocol deviations and these patients refused to undergo prostatectomy after hormonal therapy. Four patients went off protocol treatment because they were not considered surgical candidates. The racial distribution was 72% white, 20% black, 7% Hispanic and 2% Asian. Clinical stage at diagnosis was T3 in 97% and T4 in 3% of cases. Of the patients 39% were diagnosed with bulky disease. Of the 61 eligible patients 55 (90%) underwent a prostatectomy. The 5-year progression-free survival estimate was 70% (24 of 61 cases failed) and the 5-year survival estimate was 90% (11 of 61 deaths). Most of the patients in this trial would have been considered inoperable and referred to radiation oncology.

Conclusions: Neoadjuvant hormonal therapy followed by radical prostatectomy is reasonable and appropriate for clinical stage T3 prostate cancer. A progression-free and overall 5-year survival of 70% and 90%, respectively, compares favorably to Radiation Therapy Oncology Group neoadjuvant trial outcomes for this stage of prostate cancer.

KEY WORDS: prostatic neoplasms, prostatectomy, neoadjuvant therapy

The treatment for locally advanced prostate carcinoma without clinical evidence of metastasis has evolved with time. Beginning in 1944 when Vallett performed a radical prostatectomy following bilateral orchietomy[1] and later others[2,3] who added estrogen therapy before surgery, the outcome was considered successful and worthy of further study. However, these were single institution studies with small samples sizes. A retrospective review of the pre-prostate specific antigen (PSA) ERA demonstrated a 5-year survival rate without evidence of cancer of 61.5%.[4]

Since the advent of PSA monitoring of disease-free survival, there has been considerable debate about the use of neoadjuvant hormonal therapy followed by radical prostatectomy especially for clinically organ confined disease.[5] However, use and outcome for the combination of neoadjuvant therapy followed by surgery are less well defined for clinically locally advanced prostate carcinoma. Radiation oncologists have demonstrated efficacy and improved survival for the combination neoadjuvant hormonal therapy and radiotherapy compared to radiotherapy alone for clinical stage T3/T4 disease, and such an approach is considered standard of care for this high risk stage.[6–9] An important question that remains is the length of duration of neoadjuvant therapy. Gleave et al are currently investigating the question, and it appears from their data that greater than 3 months of neoadjuvant therapy followed by surgery is optimal.[10]

In the early nineties when we initiated this multiinstitutional study, there was considerable debate about the duration of neoadjuvant therapy. It was agreed that 3

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Editor's Note: **This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2192 and 2193.**

months were inadequate and perhaps 6 months were too long and may allow hormone independent clones to dominate the cancer cell population and disseminate. Therefore, 4 months of neoadjuvant therapy were elected for the study. This study was designed to test the hypothesis that neoadjuvant androgen depression before radical prostatectomy in patients with T3/T4 cancer has a clinically significant impact on relevant clinical end points. Primary end points evaluated were the cancer resectability rates, clinical response as assessed by serum PSA, digital rectal examination, transrectal ultrasound and pathological findings, and progression-free and overall survival.

METHODS

Patient population. Patients with a histologically proven initial diagnosis of clinical stage T3 prostate cancer (T3, T4 N0 and M0) were included in the study. Pelvic nodal involvement had to be excluded by computerized tomography (CT), magnetic resonance imaging (MRI) or lymphangiogram. Patients had to have bidimensionally measurable disease by transrectal ultrasound of the prostate and a baseline PSA obtained before registration. Cases were stratified into bulky and nonbulky disease by transrectal ultrasound, digital rectal examination or cystoscopy. Tumor greater than 4 cm. in diameter or invasion of the bladder on transrectal ultrasound or cystoscopy, or greater than 50% of prostate gland involved was defined as bulky disease. Nonbulky disease was defined as 4 cm. or less in diameter on transrectal ultrasound. Transrectal ultrasound was performed before study, and at 9 and 17 weeks of the study. Digital rectal examination was performed before study and at 5, 9, 13 and 17 weeks of the study.

Patients must not have received any prior treatment directed at control of prostate carcinoma, including but not limited to partial or total androgen blockade (such as bilateral orchiectomy, diethylstilbestrol, Zoladex or flutamide), radiation and surgery (such as transurethral resection of the prostate). Those patients who did undergo prostatectomy could not have additional treatment before biochemical failure. Patients must have had adequate hematologic, hepatic and renal function. Surgical candidate criteria were surgical clearance by cardiology or internal medicine consultation, no significant history of cardiovascular disease, age less than 71 years, and Southwest Oncology Group performance status 0. A resectable prostate was defined as clear delination of the lateral borders of the prostate on digital rectal examination. The proximal margin of the prostate and vesicle neck had to be distinguishable on transrectal ultrasound and/or cystoscopy such that cystectomy would not be considered preoperatively. There could be no apparent involvement of the prostate urethral junction or invasion of the external sphincter clinically.

Patients were classified by extraprostatic disease verified by imaging only (yes versus no), bulky disease (yes versus no), method to rule out pelvic nodal involvement, CT or MRI versus lymphangiogram versus CT or MRI, and lymphangiogram versus CT or MRI and/or lymphangiogram and surgery, and stage T3 versus T4.

Treatment. Neoadjuvant total androgen blockade began within 1 month after histological confirmation of diagnoses. Goserelin (3.6 mg.) was administered subcutaneously monthly for 4 months. Flutamide (250 mg.) was given orally daily (twice daily) for 4 months. Dosage modification was allowed for grade II diarrhea with a reduction of flutamide to 125 mg. twice daily. In patients with prolonged grade 3 hot flashes treatment with goserelin was withheld until symptoms diminished to grade 2 or less and then resumed. Criteria for removal from protocol treatment were unacceptable toxicity or progression of disease defined as newly appearing or measurably enlarging tumor mass in the prostate, development of ureteral obstruction with hydronephrosis, radiographically demonstrable and biopsy proven regional metastasis in the pelvis, increase PSA, appearance of bony metastasis or positive tissue diagnosis of prostate cancer outside of the soft tissue of the pelvis.

Statistics. The primary end point of the study was resectability rate. We assumed that a true resectability rate less than 40% would not be of further interest, whereas a true resectability rate of 60% or more would be of considerable interest in the treatment of stage C cancer of the prostate. A 2-stage design was used. Initially, 30 cases were accrued, and if 11 or fewer cases were resectable then the study would be permanently closed. If 12 or more cases were resectable then an additional 25 patients would be accrued. Of the 55 cases 29 or more being resectable would be evidence warranting further study provided other factors such as toxicity and survival were also favorable. This design has a significance level of 3.8% and a power of 89%. A total of 55 cases were sufficient to estimate the resectability rate and probability of response, which was 1-year progression-free survival or a particular toxicity within $\pm 13\%$ (95% CI). Progression-free survival is defined as the first evidence of biochemical, local or distant disease progression, or death in the absence of disease progression. Biochemical progression is defined as 2 PSA levels at least 3 months apart indicating an increase of 50% or more above the nadir PSA level following radical prostatectomy. All eligible patients are included in the survival and progression-free survival analyses regardless of surgery status.

RESULTS

From December 1993 to October 1996, 62 patients were accrued to this phase II clinical trial (9109). Of the 62 patients 1 was ineligible due to CT being performed outside of the protocol specified time frame, 2 refused prostatectomy following hormonal therapy and 4 did not undergo prostatectomy after 4 months of treatment because they were not surgical candidates. Thus, 55 patients completed the trial per protocol. Patients were 50 to 70 years old (median age 62.0). The racial distribution was 72% white, 20% black, 7% Hispanic and 2% Asian or Pacific Islander. The clinical stage distribution was T3 in 97% and T4 in 3% of cases. Disease was described as bulky in 39% and nonbulky in 61% of cases. Pre-study median PSA was 19.8 ng./ml. (range 2.6 to 407) and pre-study Gleason score was less than 7 in 33%, 7 in 33%, 8 in 14% and 9 to 10 in 11% of cases (table 1). Tumor size reduction detected by digital rectal examination and transrectal ultrasound was demonstrated in 98% (54 of 55) of the patients who underwent prostatectomy. Undetectable PSA,

TABLE 1. *Patient characteristics*

	Goserlin Acetate + Flutamide	
No. pts.	61	
Median pt. age (range)	62.0	(50–70)
No. race (%):		
White	44	(72)
Black (nonHispanic)	12	(20)
Hispanic	4	(7)
Asian or Pacific Islander	1	(2)
No. stage (%):		
T3	59	(97)
T4	2	(3)
No. bulky disease (%):		
Yes	24	(39)
No	37	(61)
Median pre-study PSA (range)	19.8 (2.6–407.8)	
No. pre-study Gleason sum (%):		
7 or Less	19	(33)
7	19	(33)
8	8	(14)
9–10	11	(20)