INFLUENCE OF DNA PLOIDY AND ADJUVANT TREATMENT ON PROGRESSION AND SURVIVAL IN PATIENTS WITH PATHOLOGIC STAGE T3 (PT3) PROSTATE CANCER AFTER RADICAL RETROPUBIC PROSTATECTOMY

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ABSTRACT—**Objectives.** To determine whether adjuvant treatment (AT: hormonal or radiation) affects outcome in pathologic Stage T3 (pT3) prostate cancer when analyzed according to DNA ploidy.

Methods. The predictive value of nuclear DNA ploidy and AT on clinical and prostate-specific antigen (PSA) progression and on overall and cause-specific survival after radical retropubic prostatectomy was assessed in 894 patients with pT3 prostate cancer.

Results. Mean follow-up was 6.7 years (range, 0.3 to 20). Mean age was 66 years (range, 39 to 79). Six hundred sixty patients (74%) had no immediate AT, 131 (15%) had early adjuvant radiotherapy (ART), and 103 (12%) had early adjuvant orchiectomy (AHT). DNA diploid tumors were found in 445 patients (52%), tetraploid tumors in 346 (41%), and aneuploid tumors in 59 (7%). DNA ploidy was a significant ($P < 0.05$) prognostic indicator for clinical systemic progression-free survival. With PSA progression (more than 0.2 ng/mL) as an endpoint, ploidy was an even more powerful predictor for outcome ($P = 0.004$). Use of early AHT or ART was associated with decreased overall clinical progression for diploid and nondiploid tumors ($P < 0.001$ and $P < 0.001$, respectively). With respect to PSA progression, ART and AHT were equally effective and superior to no AT only in patients with diploid tumors. However, in patients with nondiploid tumors, only AHT appeared to have improved PSA progression-free survival ($P < 0.001$) over ART or no AT, which are similar in outcome.

Conclusions. In the present nonrandomized study, AHT was as effective as ART for all endpoints except for PSA more than 0.2 ng/mL progression, for which it appeared to be superior to ART for patients with nondiploid tumors. UROLOGY® **46:** 356–364, 1995.

A significant number of patients undergoing radical retropubic prostatectomy for apparently organ-confined prostate cancer (Stage T2 or lower) have extracapsular extension, including seminal vesicle involvement or nodal disease (pathologic Stage T3 [pT3] or greater) (or both) on histopathologic examination.[1] In a nonrandomized comparative study, Cheng *et al.*[2] reviewed the influence of tumor grade and volume, seminal vesicle involvement, and margin-positive disease in the setting of adjuvant treatment (AT: orchiectomy [AHT] or radiation [ART]) or no AT after radical retropubic prostatectomy on local and systemic progression in addition to crude and cause-specific survival in patients with pT3 cancer. Nuclear DNA ploidy was not available for review at the time of the study of Cheng *et al.*

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In both univariate and multivariate analyses, only tumor grade and increasing tumor volume correlated significantly with clinical progression and cause-specific survival. AHT and ART seemed equally effective in controlling local and systemic recurrence and both were superior to no AT. However, neither crude nor cause-specific survival was significantly improved by AT.[2]

Nuclear DNA ploidy analysis in patients with pathologic Stage D1 (pT1-3, N1,2, M0) cancer has revealed a population (diploid tumors) that responds well to AHT after radical retropubic prostatectomy, with significantly improved nonprogression and survival rates in comparison with patients without AHT.[3,4]

Thus, the present study was undertaken to evaluate the inter-relationship of nuclear DNA ploidy and AT on local recurrence or systemic progression (or both) as well as on prostate-specific antigen (PSA) progression and crude and cause-specific survival. By using the same patient population as previously reported by Cheng *et al.*,[2] we are now able to provide follow-up data for a longer period for a previously well-characterized population. In

addition to including PSA (more than 0.2 ng/mL) as a measure of disease progression in these patients, we examined the use of DNA ploidy as a prognostic and stratification variable in the treatment of pT3 prostate cancer.

MATERIAL AND METHODS

A total of 894 patients (mean age, 66 years; range, 39 to 79) who underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy were found to have unequivocal pathologic Stage T3 (pT3, N0, M0) prostate cancer. This group of patients had neither preoperative hormonal manipulation nor combination postoperative AT. Among these 894 patients, 660 (74%) had no early AT (3 months or less postoperatively), 103 (12%) had postoperative AHT, and 131 (15%) had postoperative ART (6000 cGy or less) only. All AT was initiated or planned within 3 months postoperative and instituted without evidence of disease progression. ART or AHT was more often associated with patients with high-grade cancer (Gleason score 7 or higher), aneuploidy, large tumor bulk (more than 10 cm^3), seminal vesicle involvement, or margin-positive disease.

Postoperatively, patients were scheduled for follow-up evaluation at 3- to 4-month intervals for the first 2 years, semiannually for the next 2 to 3 years, and annually thereafter. Evaluation included digital rectal examination, radionuclide bone scan (with plain films when indicated), chest radiography, and PSA assay (Hybritech), beginning in 1987 when it first became available. Patients not returning to our institution were contacted annually, with additional medical information obtained from local physicians, as indicated.

Nuclear DNA ploidy assessment, as described elsewhere,[5] used a modified Hedley method[6] on paraffin-embedded tissue blocks from which nuclei were extracted, stained with fluorescent propidium iodide, and analyzed by flow cytometry.

Pathologic tumor grade is described according to the Gleason system.[7] Gleason grade 7 or higher corresponds to Mayo grade 3, 4 (high grade), and Gleason grade 4 to 6 approximates Mayo grade 2 (low grade).[8] Disease progression was defined by biopsy-proven local recurrence, evidence of metastatic disease on imaging studies, or PSA values more than 0.2 ng/mL. Local recurrence was defined as biopsy-proven prostate cancer after abnormal findings on digital rectal examination or in the search for recurrence after an increased (more than 0.2 ng/mL) PSA value, or both.

Survival data were analyzed from the date of the operation to the endpoints of local, systemic, or PSA progression as well as prostate cancer-specific death or death from all causes, using the Kaplan-Meier method.[9] The log rank test was used to evaluate the univariate association of ploidy and AT with the endpoints just described. Multivariate analysis of the effect of these factors on survival when adjusted for grade and tumor bulk was with the Cox proportional hazards regression model. The interaction between treatment and ploidy was also assessed to evaluate treatment effects within particular ploidy groups.

RESULTS

The mean follow-up period for the 894 study patients was 6.7 years (range, 0.3 to 20). Table I summarizes the distribution of patients within the AT groups, as examined by clinical stage, tumor grade, seminal vesicle involvement, and DNA ploidy. Ploidy data were unavailable for 44 (less than 5%) patients, 37 of whom received no AT, 3 received ART only, and 4 received AHT only. Of the 850 patients for whom ploidy data were available, 445 (52%) had diploid tumors, 346 (41%) had tetraploid tumors, and 59 (7%) had aneuploid tumors. High-grade (Gleason 7 or higher) tumors were noted in 40% of all patients. Figure 1 shows the association of tumor grade with DNA ploidy groups ($P < 0.001$).

Local Recurrence

The impact of ploidy on local recurrence rates was not significant ($P = 0.26$) (Fig. 2). In multivariate analysis, tumor grade and treatment were the only significant predictors of local recurrence. Nuclear DNA ploidy was not significant, and there was no significant treatment by ploidy interaction (that is, the effect of treatment was similar within each ploidy group). Five-year local recurrence-free survival rates for patients with diploid tumors were 98% for AHT and ART and 87% for no AT ($P = 0.002$). For patients with nondiploid tumors, the 5-year survival rates were 95% for AHT, 98% for ART, and 86% for no AT ($P < 0.001$).

Systemic Progression

The impact of ploidy was significant ($P = 0.011$) with respect to systemic progression (radiographic evidence or biopsy-proven evidence of metastatic disease or both). Five- and 10-year systemic progression-free survivals were 92% and 82%, respectively, for patients with diploid tumors and 91% and 81%, respectively, for those with tetraploid tumors (Fig. 3). Only 3 patients with aneuploid tumors were still under observation at 10 years. Systemic progression-free survival for these patients at 5 and 10 years was 84% and 47%, respectively. However, it is of interest that no clinical systemic progression has been observed in the 40 patients with diploid tumors who had AHT. Multivariate analysis found tumor bulk, grade, treatment, and ploidy (aneuploid versus diploid) to be significant independent predictors of systemic progression (Table II). There was no significant treatment by ploidy interaction.

Local Recurrence or Systemic Progression Combined

Nuclear ploidy as a predictor for clinical local recurrence or systemic progression was marginally significant ($P = 0.046$) (Fig. 4). ART and AHT appeared to have a significant impact over no AT with regard to overall progression (local or systemic or both) in patients with diploid and in those with nondiploid tumors ($P < 0.001$ for both groups). In patients with nondiploid tumors, ART and AHT patients had similar clinical progression-free survival rates. Multivariate analysis found tumor bulk, grade, and treatment to be significant independent predictors

TABLE I. *Age and tumor characteristics of 894 patients with pathologic Stage C (pT3) prostate cancer by early adjuvant treatment*

	Early* Adjuvant Treatment			
	None (n = 660)	Radiation Only (n = 131)	Orchiectomy Only (n = 103)	Total (n = 894)
Age (yr)				
Median	66	65	67	66
Range	39–79	43–75	52–79	39–79
Clinical stage (%)				
T1a	< 1	< 1	< 1	< 1
T1b	3	4	3	3
T1c	1	3	1	2
T2a	26	18	17	24
T2b/c	54	51	57	54
T3	15	23	22	17
Missing (no.)	1	0	0	..
Tumor bulk (%)				
≤3.0 cm^3	30	22	13	27
>3.0–10 cm^3	41	36	34	39
>10.0 cm^3	29	42	53	34
Missing (no.)	27	11	7	45
Grade (%)				
Gleason ≤6	65	51	41	60
Gleason ≥7	35	49	60	40
Seminal vesicle involvement (%)				
No	57	63	42	56
Yes	43	37	58	44
Margin-positive disease (%)				
None	78	24	36	65
Microscopic (R1)	21	66	43	30
Macroscopic (R2)	1	11	21	5
Ploidy (%)				
Diploid	55	51	40	52
Tetraploid	39	41	48	41
Aneuploid	6	8	11	7
Unknown (no.)	37	3	4	44

**Within 90 days postoperatively.*

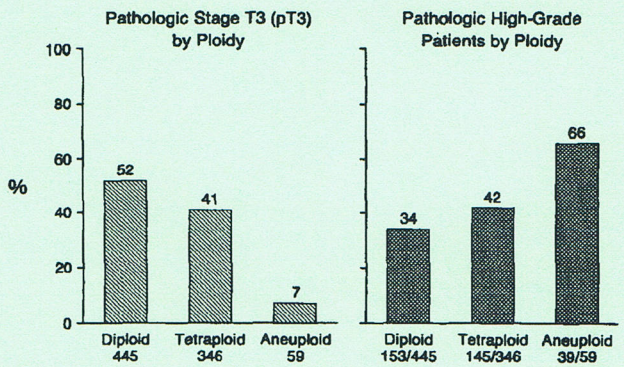

FIGURE 1. *Ploidy analysis of pathologic stage T3 (pT3) tumors after radical prostatectomy. Proportion of patients in each ploidy group with high-grade prostate cancer.*

of clinical local recurrence or systemic progression, or both. However, DNA ploidy was not significant when adjusted for these variables. Again, there was no significant ploidy by treatment interaction.

Local Recurrence, Systemic Progression, or Prostate-Specific Antigen More Than 0.2 ng/mL

Nuclear DNA ploidy was highly significant across all AT groups when PSA values more than 0.2 ng/mL were considered as endpoints for progression in addition to local recurrence or systemic progression (or both) ($P = 0.004$) (Fig. 5). Five- and 10-year progression-free survivals in patients with diploid tumors (63% and 42%, respectively) were similar to those with tetraploid tumors (58% and 38%, respectively). This was in contrast to patients with aneuploid tumors who had only 43% progression-free survival at 5 years; only 1 survivor was under observation at 10 years. Multivariate analysis (Table II) found all variables to be significant. In addition, there was a suggestion of a significant treatment by ploidy interaction ($P = 0.065$).

In contrast to the data derived from only clinical or radiographic information, the addition of PSA more than 0.2 ng/mL as an endpoint for progression revealed differential AT effects between diploid and nondiploid tumors. Patients with

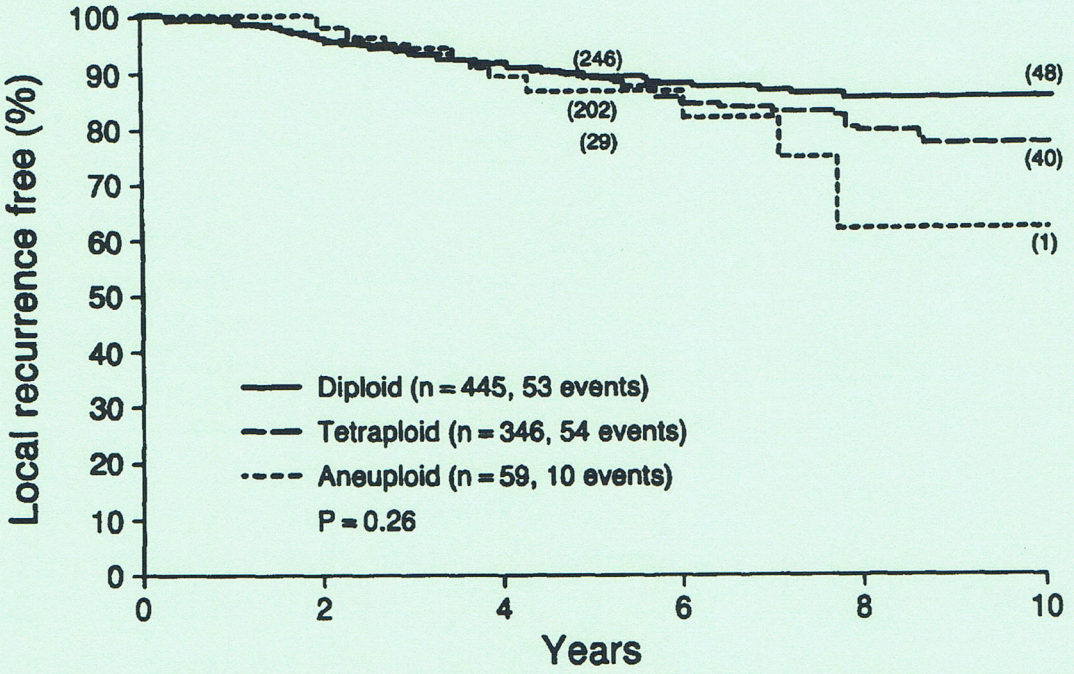

FIGURE 2. *Impact of ploidy on survival free of local recurrence. Numbers in parentheses are the number at risk at 5 and 10 years.*

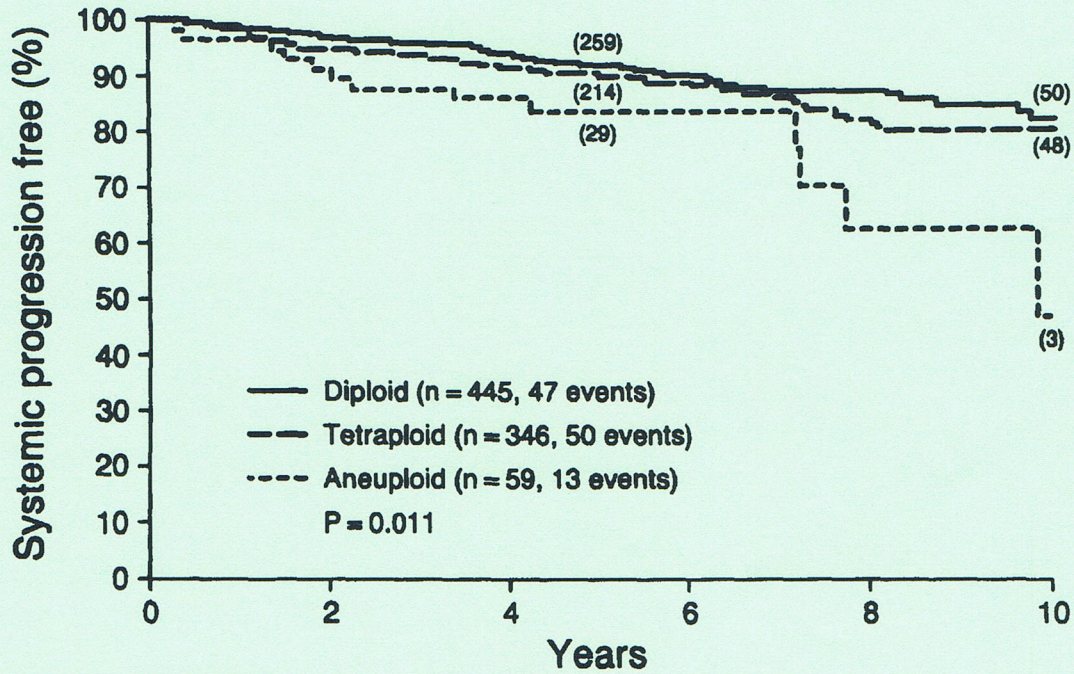

FIGURE 3. *Impact of ploidy on survival free of clinical systemic progression. Numbers in parentheses are the number at risk at 5 and 10 years.*

diploid tumors who had ART or AHT, in comparison with those who had no AT, had similar significantly improved ($P < 0.001$) progression-free survival (Fig. 6). The 5- and 10-year progression-free survival rates for AHT patients were 81% and 65%, respectively, and 72% and 63%, respectively, for ART patients. The rates for patients with diploid tumors who received no AT were 59% and 35%, respectively. Among patients with nondiploid tumors, progression-free survival rates for those receiving AHT, ART, or no AT differed significantly ($P < 0.001$) (Fig. 7). Nondiploid tumor patients undergoing AHT had an 85% and 81% 5- and 10-year progression-free survival, respectively. However, patients receiving ART had significantly lower progression-free survival rates, which were similar to the results of those with no AT: 5- and 10-year progression-free survival was

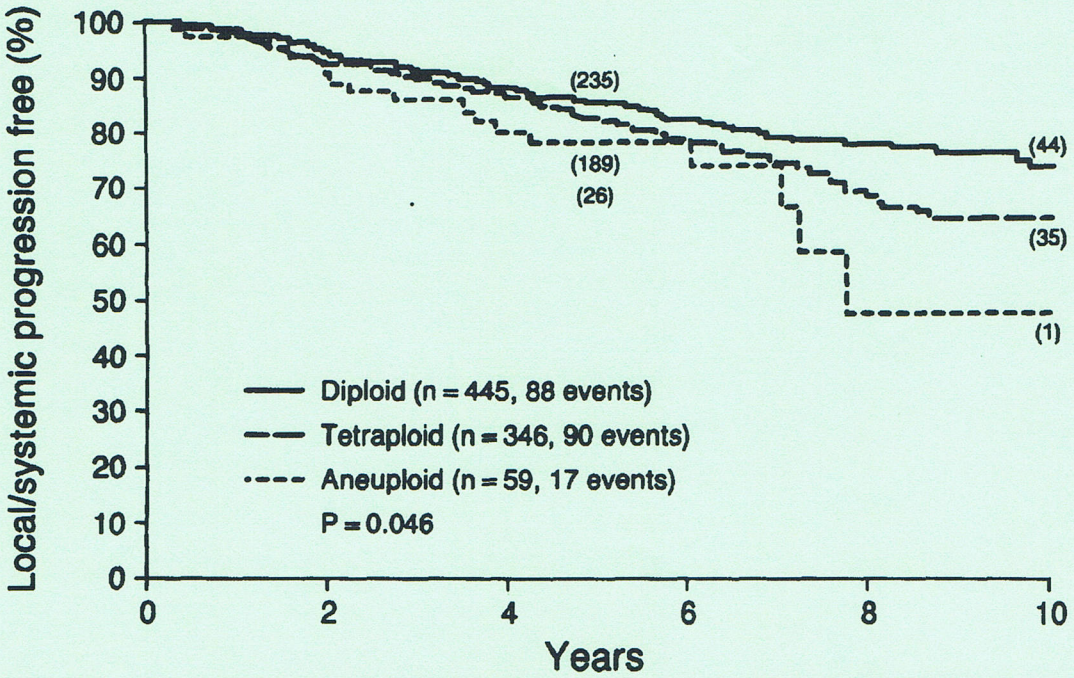

FIGURE 4. *Impact of ploidy on survival free of clinical local recurrence or systemic progression. Numbers in parentheses are the number at risk at 5 and 10 years.*

TABLE II. ***Estimated relative risk for tumor bulk, grade, adjuvant treatment, and DNA ploidy on systemic progression and cause-specific death****

	Relative Risk (95% Confidence Interval)		
Risk Factor	**Systemic Progression**	**Systemic Progression or PSA > 0.2 ng/mL**	**Cause-Specific Death**
Tumor bulk (per cm^3 increase)	1.02 (1.01–1.03)†	1.02 (1.01–1.03)†	1.02 (1.01–1.04)†
Grade (high versus low)	2.11 (1.39–3.21)†	2.26 (1.83–2.79)†	2.20 (1.23–3.94)†
Adjuvant therapy			
ART versus none	0.45 (0.22–0.90)†	0.53 (0.39–0.73)†	0.24 (0.06–0.98)†
AHT versus none	0.13 (0.04–0.43)†	0.15 (0.09–0.25)†	0.11 (0.01–0.78)†
DNA ploidy‡			
Tetraploid versus diploid	1.26 (0.83–1.92)	1.14 (0.93–1.41)	1.61 (0.90–2.87)
Aneuploid versus diploid	2.07 (1.09–3.95)†	1.54 (1.07–2.22)†	1.40 (0.50–3.97)

KEY: AHT = adjuvant orchiectomy; ART = adjuvant radiotherapy; PSA = prostate-specific antigen.

**Based on Cox proportional hazards regression model, including all tabled risk factors. The estimated relative risk is the ratio of the event rate for those with the risk factor relative to those without the risk factor. There were 811 patients with complete data for this analysis, including 103 who had systemic progression, 188 with systemic progression or PSA >0.2 ng/mL, and 55 who died of prostate cancer.*

†*P <0.05 for test of the hypothesis that the true relative risk is 1.00.*

‡*The interaction between treatment and ploidy (diploid versus nondiploid) was investigated and found to be marginally significant (P = 0.065 on 2 d.f.) only for the PSA endpoint.*

60% and 42%, respectively, for patients who had ART and 50% and 28%, respectively, for those who had no AT.

CAUSE-SPECIFIC SURVIVAL

Ploidy was not a significant univariate predictor of cause-specific survival when independently measured across all treatment groups in univariate analysis ($P = 0.15$) (Fig. 8). It also was not significant in multivariate analysis, although the confidence intervals were quite wide because of the relatively small number of deaths (Table II). Patients who had ART and those who had AHT had significantly better survival rates when compared to no AT, using multivariate analysis. Evaluation of the interaction terms in multivariate analysis suggested that the effect of treatment on cause-specific survival was similar in patients with diploid tumors and in those with nondiploid tumors.

Cause-specific survival rates by treatment group began to separate at about 7 years after radical retropubic prostatectomy, and at 10 years, the rates were 84% for the no AT group, 98% for the ART group, and 95% for the AHT group (Fig. 9). The number of patients under observation at 10 years in the ART and AHT groups was small (8 patients in each group); hence, this result must be considered tentative.

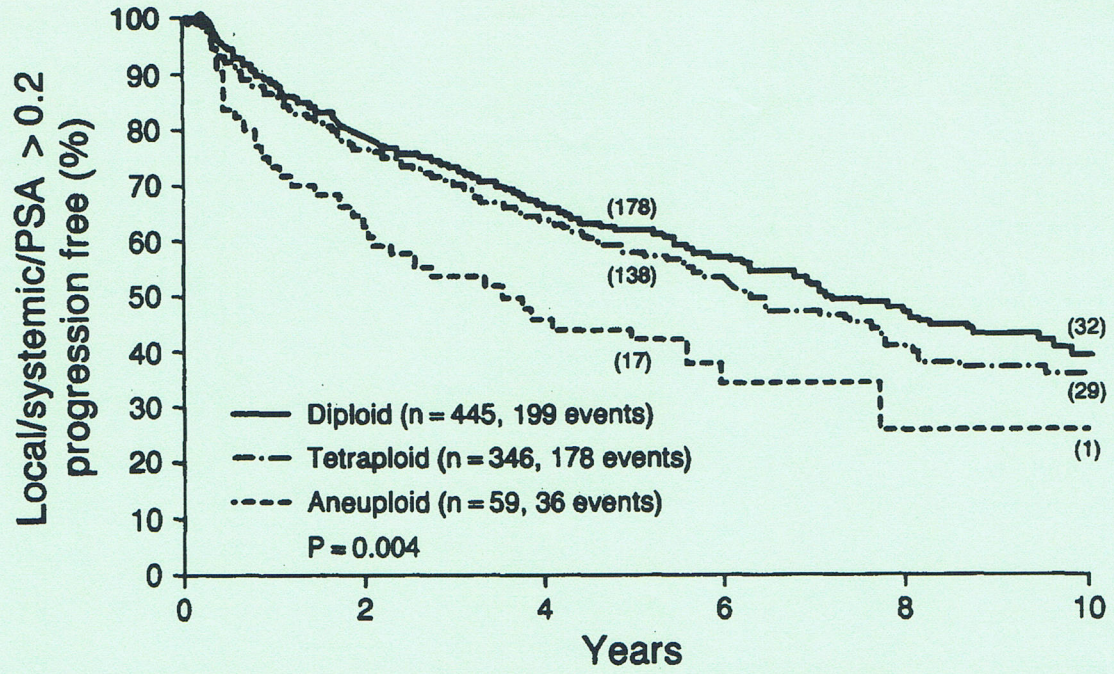

FIGURE 5. *Impact of ploidy on survival free of local recurrence, clinical systemic progression, or PSA > 0.2 ng/mL. Numbers in parentheses are the number at risk at 5 and 10 years.*

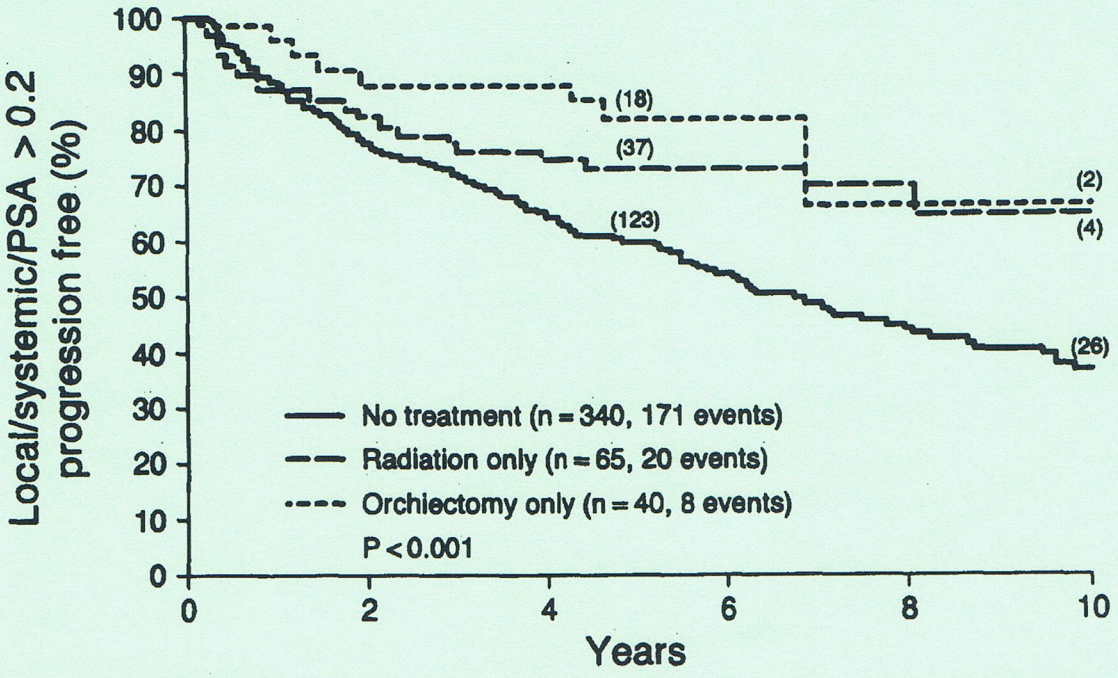

FIGURE 6. *Impact of treatment on survival free of local recurrence, clinical systemic progression, and/or PSA > 0.2 ng/mL among diploid tumors. Numbers in parentheses are the number at risk at 5 and 10 years.*

COMMENT

At radical retropubic prostatectomy for clinically localized prostate cancer, about half of the patients have extracapsular prostate cancer.[1-5,10-12] This number may be smaller in screened populations.[13] Available data suggest that some patients with pathologic pT3 disease have a more favorable course than others.[5,14] AT has been associated with improved disease-free survival,[15,16] and ART after radical prostatectomy can be associated with debilitating urinary incontinence.[17] An earlier study of 49 patients with pT3 prostate cancer suggested improved progression-free survival with AHT and ART after radical retropubic prostatectomy.[15] Morgan *et al.*[16] described reduced PSA values 1 year after radical retropubic prostatectomy in patients who underwent ART for pT3 prostate cancer. Clinical disease-free survival (PSA excluded) after radical retropubic prostatectomy and ART for pT3 prostate cancer in doses of 33 to 62 Gy (median, 45) was 94% and 87% at 5 and 10 years, respectively.[18] However,

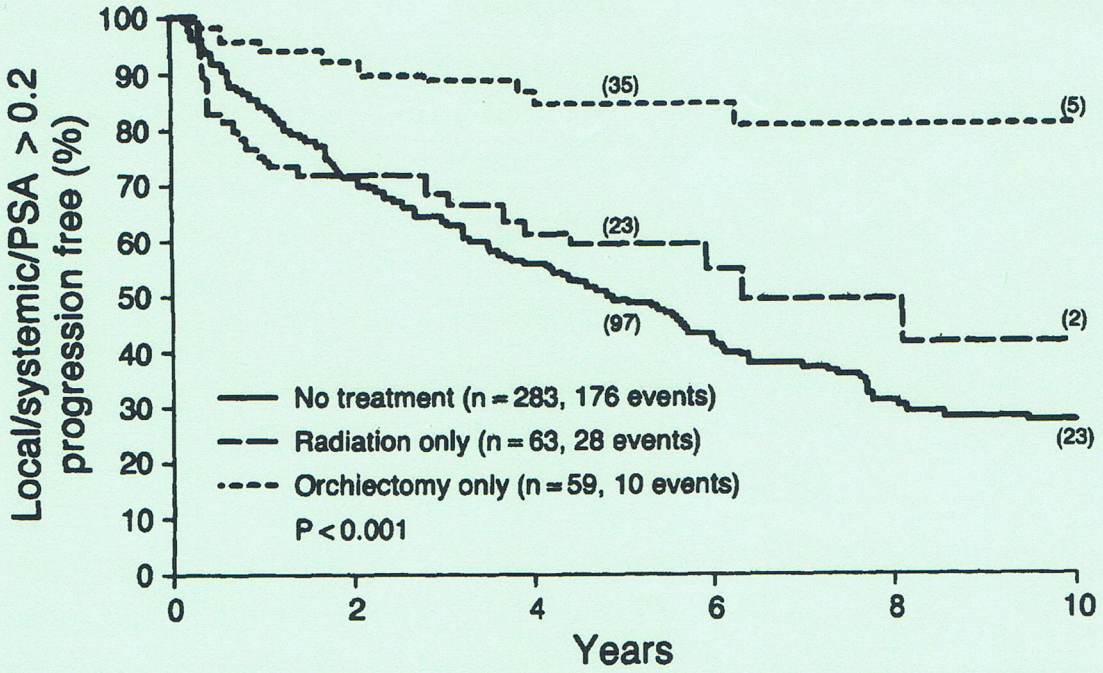

FIGURE 7. *Impact of treatment on survival free of local recurrence, clinical systemic progression, and/or PSA >0.2 ng/mL among nondiploid tumors. Numbers in parentheses are the number at risk at 5 and 10 years among nondiploid tumors.*

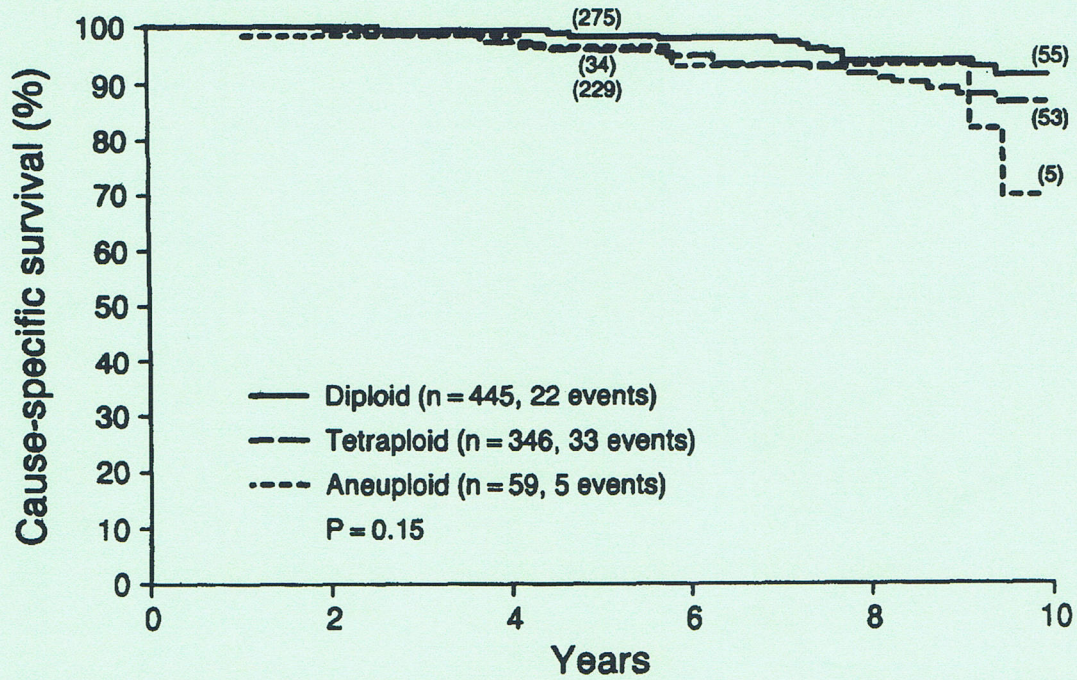

FIGURE 8. *Impact of ploidy on cause-specific survival. Numbers in parentheses are the number at risk at 5 and 10 years.*

the inclusion of detectable postoperative PSA values as a measure of progression decreased disease-free survival rates after radical prostatectomy and ART to 64% and 54% at 5 and 10 years, respectively,[18] with a worse prognosis for those patients who had high-grade tumors or seminal vesicle involvement.[11,18] Therefore, a manner by which patients with potentially more aggressive disease can be selected and treated against the natural history of their particular prostate cancer would be appropriate. The present data suggest an avenue of investigation that warrants further evaluation.

Nuclear DNA ploidy has been useful in predicting the natural history and treatment of pathologic Stage pT1-3, N1, M0 prostate cancer,[4] in which patients with diploid tumors have demonstrated improved rates of nonprogression after radical retropubic prostatectomy and hormonal manipulation. In the present study, ploidy by itself was not

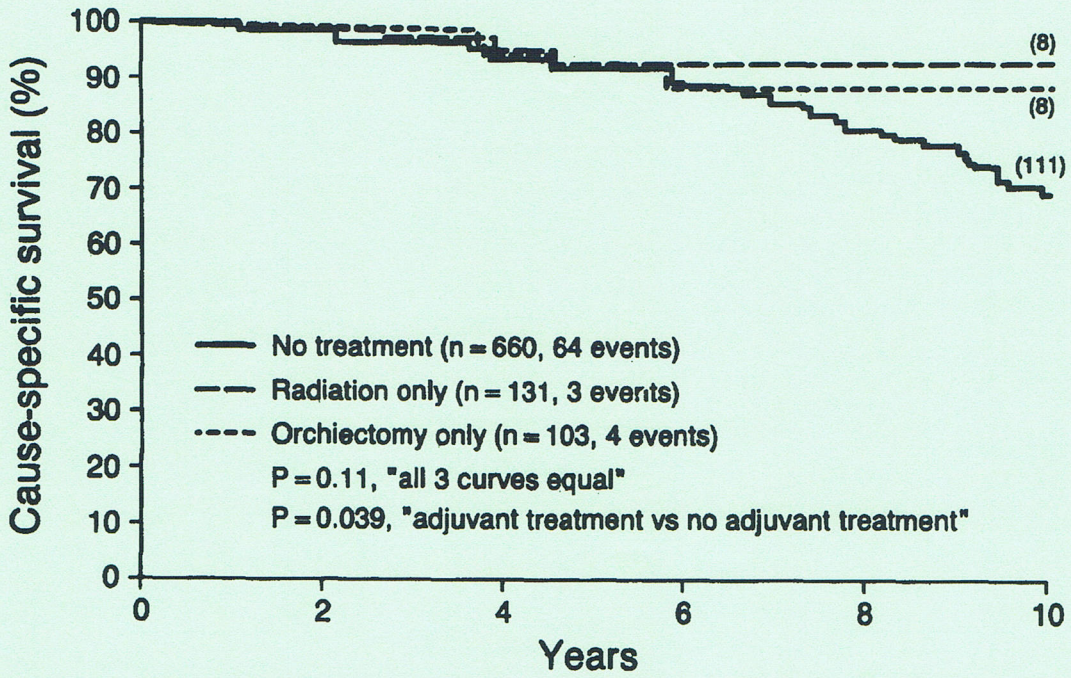

FIGURE 9. *Impact of treatment on cause-specific survival. Numbers in parentheses are the number at risk at 5 and 10 years.*

significant in predicting cause-specific survival ($P > 0.05$); however, in contrast to studies evaluating more advanced stage pT1-3, N1, M0 disease, the period of observation was relatively short in this study with respect to the natural history of prostate cancer death due to stage pT3 disease. It is conceivable that with a longer follow-up period, differential effects of ATs and ploidy may become apparent in disease-specific death rates.

The data herein seem to support the use of AT (hormonal or radiation) in controlling local recurrence. Local recurrence among patients who received ART or AHT was significantly lower for both diploid ($P = 0.002$) and nondiploid ($P < 0.001$) groups when compared with patients who received no AT.

Determination of ploidy alluded only to marginally significant differences in the clinical determination of local recurrence or systemic progression ($P = 0.047$). Clinical local recurrence or systemic progression-free survival rates after ART were similar to those of AHT in patients with diploid or nondiploid tumors. It is noteworthy, however, that among 40 patients with diploid tumors who underwent AHT, 98% showed no clinical local recurrence or systemic progression at 5 and 10 years. Both ART and AHT were superior to no AT in patients with diploid ($P < 0.001$) or nondiploid tumors ($P < 0.001$).

The distinction between patients with diploid tumors and those with nondiploid tumors and the potential advantages of differential AT based on ploidy became apparent when PSA more than 0.2 ng/mL was used as a criterion for disease progression. Among patients with diploid tumors, either ART or AHT offered improved progression-free survival, with 5- and 10-year progression-free survival rates of 72% and 63%, respectively, for the ART group and 81% and 65%, respectively, for the AHT group. Patients who received no AT had only a 59% and 35% 5- and 10-year PSA progression-free survival, respectively ($P < 0.001$).

However, in patients with nondiploid tumors, ART conferred no PSA progression-free survival advantage over no AT, whereas patients with nondiploid tumors who had AHT had an 85% and 81% 5- and 10-year progression-free survival, respectively ($P < 0.001$). Previous studies have suggested that AHT masks or inhibits PSA progression[19]; however, this would not entirely explain the differential results after AHT between patients with diploid tumors and those with nondiploid tumors. One may speculate that nondiploid tumors, having a more aggressive biologic potential, have metastasized in an occult fashion to where they are no longer treated (controlled) by regional therapy such as radiation, thus accounting for the increasing PSA values, which are detected before the overt clinical endpoints described earlier. These data also support the findings in clinical practice that about 50% of patients respond to ART, which is similar to the incidence of diploidy in the group of patients with pT3 disease.

CONCLUSIONS

In the present nonrandomized study, AHT was as effective as ART for all endpoints except local or

systemic or PSA progression more than 0.2 ng/mL, for which it appeared to be superior to ART for patients with nondiploid tumors. To evaluate this hypothesis definitively, prospective randomized trials need to be conducted. One may expect that the trends noted in PSA progression portend future clinical findings. The current study suggests that future AT protocols consider PSA evaluation as an outcome measure and stratify for DNA ploidy.

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