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Evaluation of Adjuvant Estramustine Phosphate, Cyclophosphamide, and Observation Only for Node-Positive Patients Following Radical Prostatectomy and Definitive Irradiation

Joseph D. Schmidt, Robert P. Gibbons, Gerald P. Murphy, Alfred Bartolucci, and the Investigators of the National Prostate Cancer Project

Division of Urology, University of California, San Diego School of Medicine, La Jolla, California (J.D.S.); Department of Urology, Virginia Mason Medical Center (R.P.G.); Pacific Northwest Cancer Research Foundation (G.P.M.), Seattle, Washington; Department of Biostatistics and Biomathematics, University of Alabama at Birmingham (A.B.)

ABSTRACT: In 1978 the National Prostate Cancer Project launched two protocols evaluating adjuvant therapy following surgery (Protocol 900) or irradiation (Protocol 1,000) for clinically localized prostate cancer. All patients underwent staging pelvic lymphadenectomy. Following definitive treatment, patients were randomized to either cyclophosphamide 1 gram/m^2-IV every 3 weeks for 2 years, estramustine phosphate 600 mg/m^2-po daily for up to 2 years, or to observation only. Patient accession closed in 1985 and includes 184 to Protocol 900 (170 evaluable) and 253 to Protocol 1,000 (233 evaluable). Lymph node involvement was identified in 198 patients (49% of total), 29% in Protocol 900, 63% in Protocol 1,000.

Median progression-free survival (PFS) for patients with nodal involvement in Protocol 1,000 receiving estramustine phosphate adjuvant was longer (37.3 mo) compared to cyclophosphamide (30.9 mo) and to no treatment (20.9 mo). Median PFS for patients with limited nodal disease in Protocol 1,000 was longer (39.9 mo), regardless of adjuvant, compared to extensive nodal disease (20.7 mo). However for patients with extensive nodal involvement, those receiving adjuvant estramustine phosphate experienced a significantly longer median PFS (32.8 mo) compared to adjuvant cyclophosphamide (22.7 mo) and no adjuvant (12.9 mo). We conclude that adjuvant estramustine phosphate is of benefit in prostate cancer patients with extensive pelvic node involvement receiving irradiation as definitive treatment.

KEY WORDS: **Stage D1 prostate cancer, pelvic lymphadenectomy, progression-free survival**

INTRODUCTION

Under the auspices of the United States National Cancer Institute, the National Prostatic Cancer Project (NPCP), later renamed National Prostatic Cancer Treatment Group (NPCTG), in 1978 initiated two randomized prospective studies evaluating the efficacy of adjuvant treatment following either radical surgery (Protocol 900) or definitive irradiation (Protocol 1,000). All eligible patients entered had localized and potentially curable prostate cancer and underwent pelvic lymph node dissection. Clinical stages A

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Address reprint requests to Joseph D. Schmidt, M.D., Division of Urology (8897), UCSD Medical Center, 200 West Arbor Drive, San Diego, CA 92103-8897.

and B1 were specifically excluded from the studies since any possible benefit of an adjuvant would be unlikely to have impact in these stages.

Following recovery from surgery or radiotherapy, the choice based on investigator's discretion, patients received randomized adjuvant: intravenous cyclophosphamide (Cytoxan, Bristol-Myers Company, Evansville, IN) 1 gm per meter sq every 3 weeks for up to 2 years, or estramustine phosphate (Estracyt, Emcyt, Kabi Pharmacia, Helsingbord, Sweden) 600 mg per meter sq orally in three divided doses for up to 2 years, or observation only (standard treatment). In addition to collecting adjuvant treatment toxicity data, end points of the study included time to the first evidence of recurrent disease (progression-free survival or PFS) and overall survival. This report focuses on the patient group with pelvic nodal metastases.

MATERIALS AND METHODS

At the time of closure of both Protocols in 1985, 437 patients had been accessioned. This included 184 patients into Protocol 900 and 253 patients into Protocol 1,000. Follow-up information has been available on 170 and 233 patients, respectively. Pelvic lymph node metastases (stage D-1 or N 1–3) were documented in 49% of the entire group. Nodal involvement was found in 29% of Protocol 900 patients and in 63% of Protocol 1,000 patients.

Follow-up information is now available on patients from 80–160 months with an average follow-up of 120 months or 10 years. In this report of long-term follow-up, recurrence rates, median progression-free survival, and overall survival, results in each protocol and the results of assigned adjuvant therapy are examined. Because of our previous observation that patients with less than 20% lymph node involvement (based on number of nodes with metastases) had a significantly better progression-free survival (P = 0.0002) than those with greater than 20% lymph node metastases, we examined the influence of the assigned adjuvant treatment [1,2]. Statistical analysis was done by the log-rank test controlled for the effects of protocol and treatment [3].

Recurrence (disease progression) was defined according to NPCP criteria. In nearly every instance, recurrence indicated the appearance of distant metastatic disease as documented on radionuclide bone scan. Increase of serum acid phosphatase generally accompanied changes of bone scans. More recent recurrences have been documented by changes in serum prostate-specific antigen (PSA), but baseline PSA data were not available on these patients at accession. Survival data were based on deaths due to prostate cancer.

TABLE I. NPCP Protocol 900: Recurrent Disease

Path. stage at entry	No Rx (%)[a]	Cytoxan (%)	Emcyt (%)	Total (%)
B2	1 (6)	11 (65)	6 (33)	18 (34)
C	12 (60)	12 (55)	9 (36)	33 (49)
D1	11 (79)	9 (56)	13 (72)	33 (69)
	24 (46)	32 (56)	28 (46)	84 (49)

[a]Percent of randomized patients.

RESULTS

Recurrent disease for patients in Protocol 900 is shown in Table I. The overall recurrence rate in the surgically treated population is 49%, but is 69% in the node-positive group. The rate of recurrence based on the assigned adjuvant treatment is not statistically different.

Tumor recurrence for patients entered into Protocol 1,000 (Table II) also shows a trend for increasing rates of recurrence based on the stage of disease at entry. The overall rate of recurrence in Protocol 1,000 patients is 65%, but is 81% in the node-positive group. However, the recurrence rate for node-positive patients receiving adjuvant estramustine phosphate was significantly lower at 60% compared to 81% for the no treatment arm and to 87% for patients receiving adjuvant cyclophosphamide. In both protocols, recurrence rates paralleled increasing tumor grade.

Progression-free survival (PFS) for node-positive (N+, D-1) patients in both Protocols 900 and 1,000, but with no adjuvant treatment, is compared in Figure 1.[1] The surgically treated group demonstrates a trend towards improved progression-free survival at a P value of 0.0819. A similar pattern was seen for adjuvant cyclophosphamide favoring the surgery group (P = 0.0074). However, the estramustine adjuvant PFS data were similar for both protocols (P = 0.4939).

Progression-free survival for patients with pelvic lymph node metastases in Protocol 1,000 compared to adjuvant assignment is seen in Figure 2. The longest median progression-free survival time is seen in pa-

[1]In all figures, the first column indicates protocol or assigned adjuvant treatment; second, numbers of patients in that category; third, number of patients failing (progress or death); fourth, median progression-free survival or overall survival time; fifth, comparative patients groups; sixth, log-ranked P values.

TABLE II. NPCP Protocol 1,000: Recurrent Disease

Path. stage at entry	No Rx (%)[a]	Cytoxan (%)	Emcyt (%)	Total (%)
B2	3 (43)	6 (55)	0 (00)	9 (41)
C	8 (40)	8 (62)	7 (32)	23 (42)
D1	42 (81)	45 (87)	31 (60)	118 (81)
	53 (63)	59 (77)	39 (49)	151 (65)

[a]Percent of randomized patients.

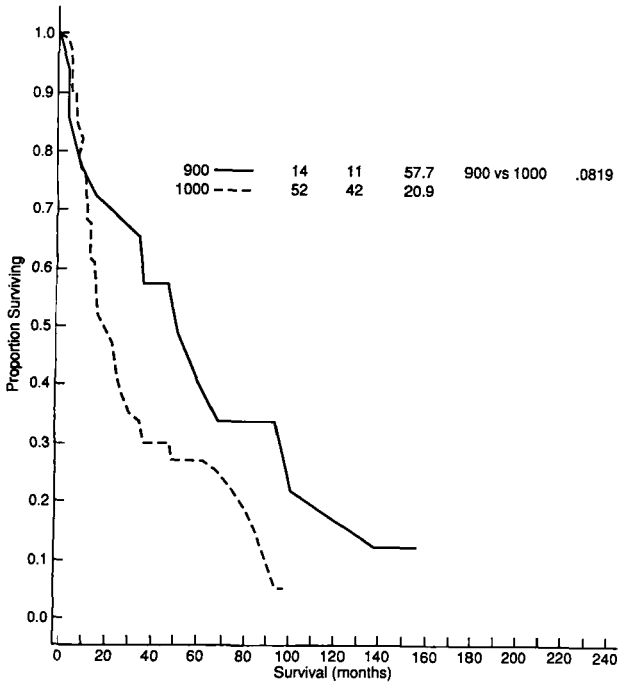

Fig. 1. Progression-free survival for observation-only patients (Stage D-1, N+)—NPCP Protocol 900 vs. 1,000.

tients receiving adjuvant estramustine phosphate (37.3 mo). However the differences do not reach statistical significance.

PFS for D-1 patients in Protocol 900 comparing adjuvant treatment is seen in Figure 3. No differences were noted in the three arms.

The relationship of the degree of lymph nodal involvement and progressive disease is seen in Table III. Patients with greater than 20% lymph node involvement have a statistically significantly greater relapse rate of 80% compared to 69% with those with less than 20% lymph node involvement. This relationship exists for both the no treatment and cyclophosphamide adjuvant groups; however patients receiving adjuvant estramustine phosphate have a similar relapse rate (71%) regardless of pelvic lymph node involvement.

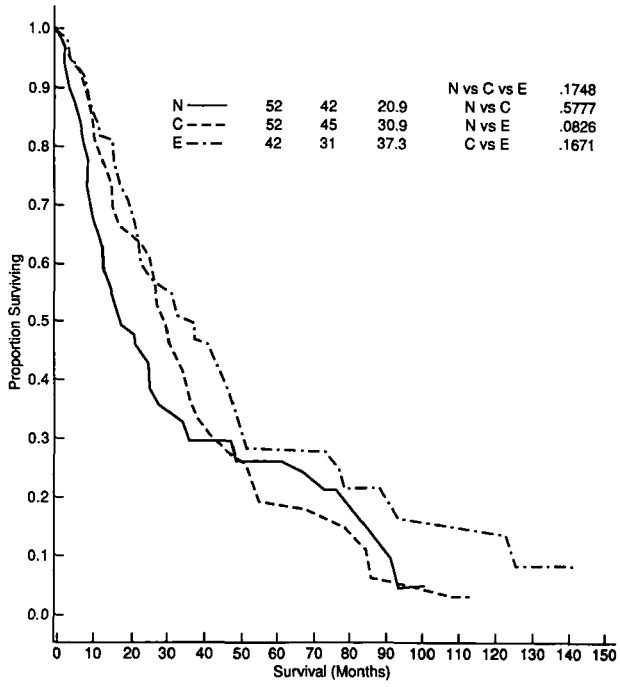

Fig. 2. Progression-free survival for patients with Stage D-1 (N+) disease NPCP Protocol 1,000. Influence of assigned adjuvant.

The progression-free survival for all patients with pelvic node metastases is seen in Figure 4. Patients with the lower tumor burden have a statistically better progression-free survival of 48.7 months with a *P* value of 0.0007. Figure 5 displays the progression-free survival for patients in Protocol 1,000 based on the degree of lymph node metastases. Patients with limited lymph node metastases had a statistically significantly greater median progression-free survival of 39.9 months with a *P* value of 0.0098. In Protocol 900, PFS was essentially similar (55.3 and 51.7 mo) for these patients (20 with limited and 24 with extensive nodal disease).

The influence of assigned adjuvant treatment for patients in Protocol 1,000 and limited nodal metastases is seen in Figure 6. There are no differences in the three groups with the best median progression-free survival being recorded for patients receiving adjuvant cyclophosphamide (42.6 months). Progression-free survival for patients in Protocol 1,000, having greater than 20% lymph node involvement compared to adjuvant treatment, is seen in Figure 7. The longest median PFS time is recorded for the estramustine phosphate group at 32.8 months with *P* values as shown. In Protocol 900, patients with extensive nodal disease receiving adjuvant estramustine phosphate showed the greatest PFS (55.3 mo compared to 39.5 mo for cyclophosphamide, and 36.7

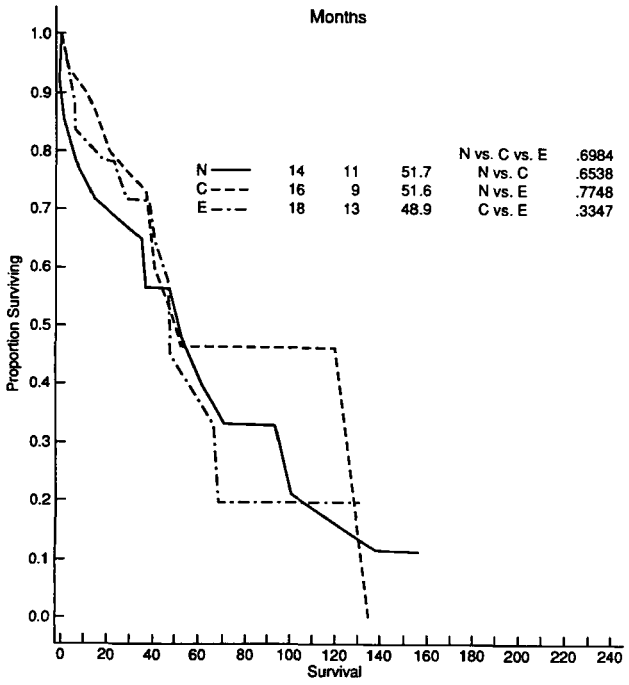

Fig. 3. Progression-free survival for patients with Stage D-I (N+) disease NPCP Protocol 900. Influence of assigned adjuvant.

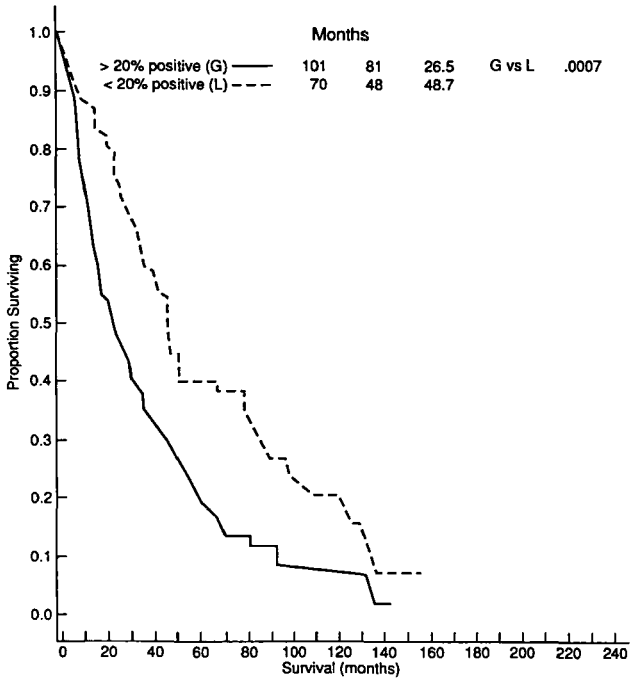

Fig. 4. Progression-free survival for patients NPCP Protocols 900 and 1,000 with Stage D-I (N+) disease. Influence of degree of nodal metastases.

TABLE III. Recurrent Disease in Patients With Nodal Metastases (Stage D-I, N I–3) by Degree of Metastases and Assigned Adjuvant

	<20% Relapse/ total (%)[a]	>20% Relapse/ total (%)[a]	Chi-Square *P*-value
No Rx	17/25 (68)	28/33 (85)	0.128
Cytoxan	21/31 (68)	26/30 (87)	0.079
Emcyt	10/14 (71)	27/38 (71)	0.979
Total	48/70 (69)	81/101 (80)	0.040

[a]Percent of randomized patients.

mo for no treatment) but these data are not statistically significant.

The PFS for all node-positive patients regardless of adjuvant assignment is seen in Figure 8.

Survival Data

The influence of surgery as the major determining factor in survival is noted in Figure 9. Similar data for each of the three adjuvant assignments reflects the longer survival for Protocol 900 patients. Median survival time has not yet been reached for patients with node-positive disease treated with prostatectomy.

In Protocol 1,000, estramustine phosphate adjuvant is associated with the greatest median survival time (138.9 mo), but as yet the data are not statistically significant (Fig. 10). For Protocol 900 node-positive patients, there are as yet no apparent differences for the three adjuvant groups, and median survival time for these 48 patients has not been reached.

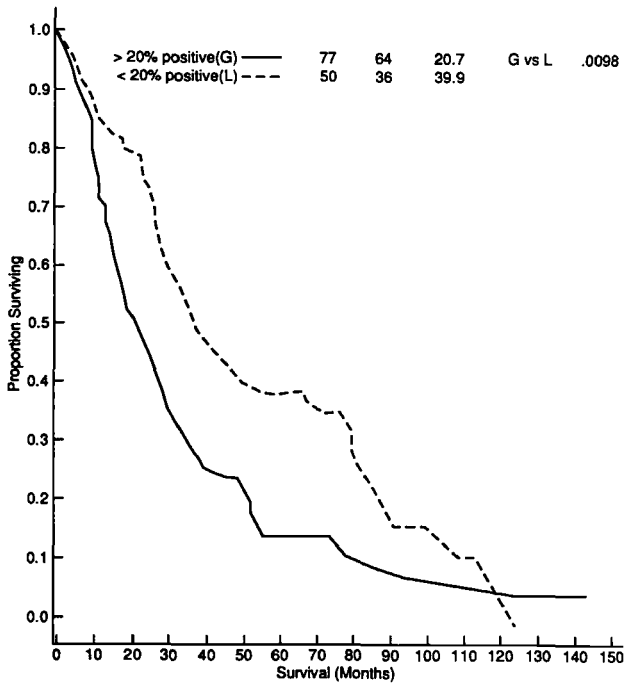

Fig. 5. Progression-free survival for Stage D-I (N+) patients NPCP Protocol 1,000. Influence of degree of nodal metastases.

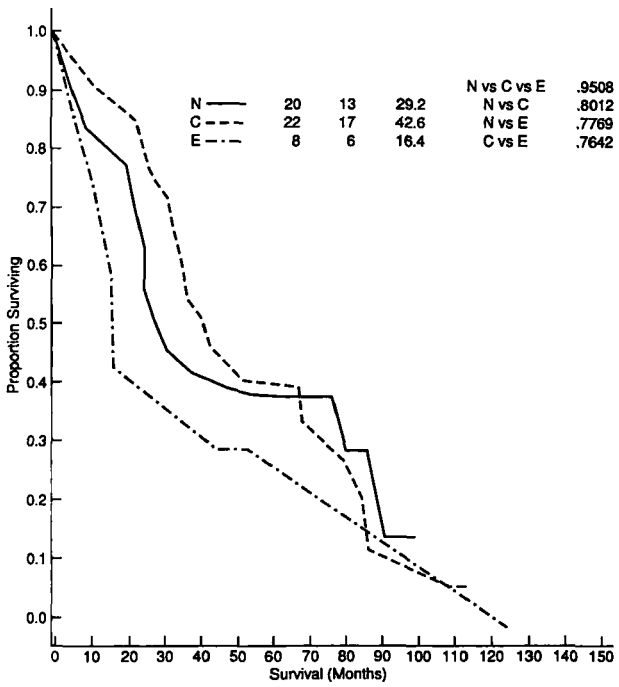

Fig. 6. Progression-free survival for Stage D-1 (N+) patients NPCP Protocol 1,000 with minimal nodal metastases (<20%). Influence of assigned adjuvant.

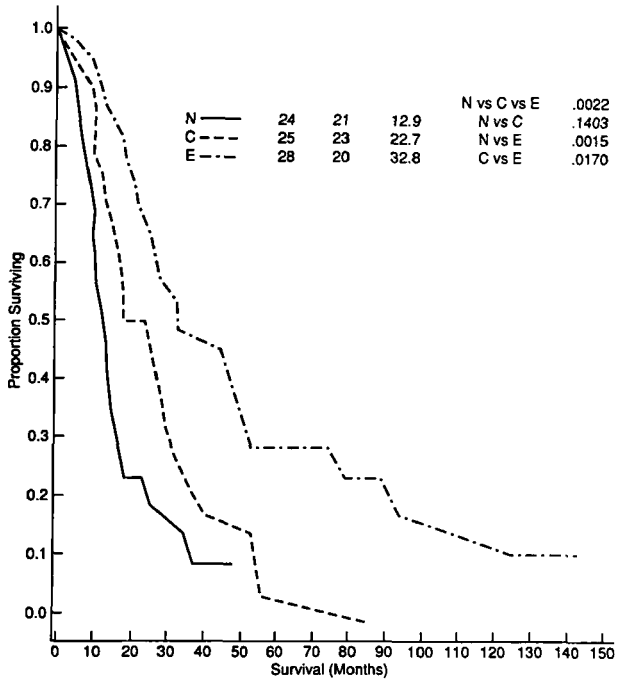

Fig. 7. Progression-free survival for Stage D-1 (N+) patients NPCP Protocol 1,000 with marked nodal metastases (>20%). Influence of assigned adjuvant.

DISCUSSION

For these two protocols the investigators of the NPCP chose estramustine phosphate and cyclophosphamide as adjuvants because of the relative safety and efficacy of these agents when used in patients with advanced disease either as primary or secondary treatment [4,5]. Interestingly, the concept of combining drug therapy and radical prostatectomy in an attempt to improve patient response is not new [6]. More recently, the Mayo Clinic data have stressed the role of adjuvant treatment, specifically orchiectomy, for patients with pelvic lymph node metastases undergoing radical prostatectomy or local irradiation [7]. In fact their data demonstrate that patients receiving adjuvant orchiectomy and having diploid tumors have a survival equal to, if not greater than, age-matched controls.

The influence of pelvic nodal metastases as a prognostic sign has been discussed by many authors. Some have reported that any involvement of pelvic lymph nodes with metastatic cancer is associated with decreased PFS and overall survival [8–10]. On the other hand, the concept that minimal node involvement may be consistent with a better PFS and overall survival equal to that of the primary tumor has been shown by others [11–13].

In the data presented, overall survival and progression-free survival are better in patients in the surgical protocol (900), likely reflecting inherent selection based on the stage and grade of disease. Again

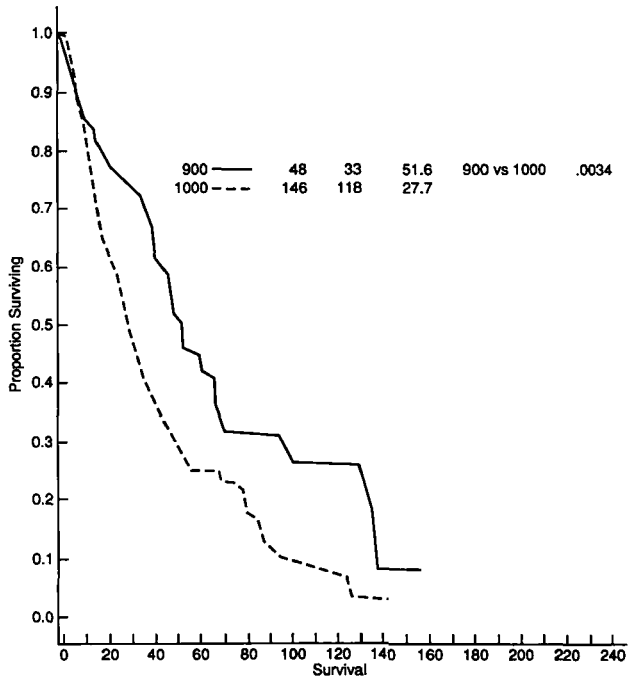

Fig. 8. Progression-free survival for all Stage D-1 (N+) patients NPCP Protocol 900 and 1,000.

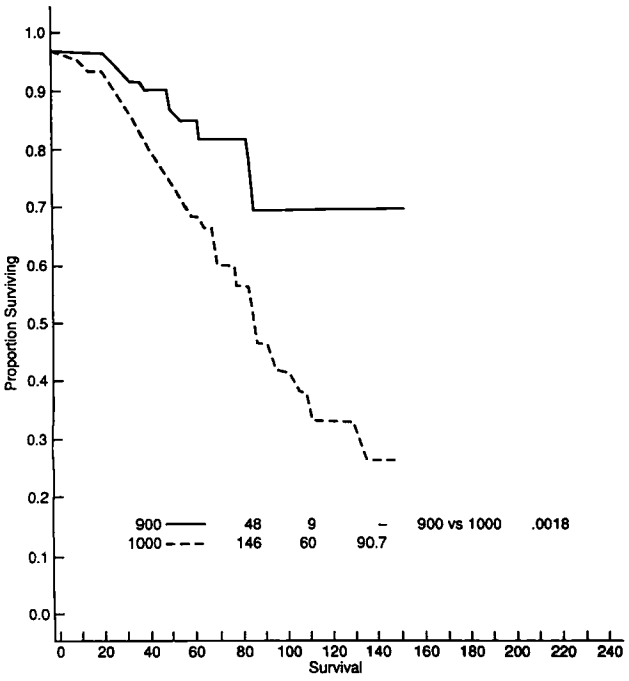

Fig. 9. Survival for all node-positive patients—NPCP Protocol 900 vs. 1,000.

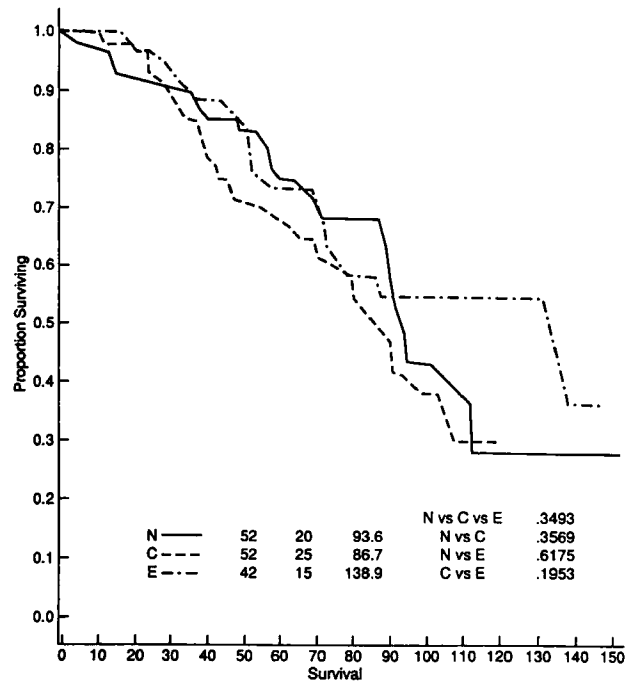

Fig. 10. Survival for node-positive patients in NPCP Protocol 1,000. Influence of assigned adjuvant.

note the greater number of patients with pelvic lymph node metastases in the irradiation (63 vs. 29%) protocol. Although recurrent disease has now been seen in 69% of the node-positive patients receiving radical surgery (Protocol 900) and in 81% of the node-positive patients receiving definitive radiotherapy (Protocol 1,000), many of these patients are surviving, thus making comments on overall survival differences premature.

The beneficial effect of estramustine phosphate as an adjuvant, seen particularly in patients in Protocol 1,000 with greater lymph node involvement, is of extreme interest. Whether this effect is related to the estrogenic (estradiol) properties of the drug or to its more recently discovered cytotoxic anti-microtubular properties cannot yet be determined [14,15]. However, this apparent benefit from adjuvant estramustine phosphate has not been seen in Protocol 1,000 patients with minimal lymph node involvement nor in patients receiving radical prostatectomy (Protocol 900), although only 48 patients are included in the latter group. Selection criteria favoring more low stage patients undergoing radical prostatectomy may obscure any possible benefit of an adjuvant drug. For example, in this study only 48 patients with nodal disease were subjected to radical prostatectomy compared to 146 undergoing definitive irradiation. Similarly, patients with minimal pelvic lymph node metastases may show no appreciable enhancement of their response to primary treatment with any currently available adjuvant.

CONCLUSIONS

From the data presented here we conclude that:

1) Progression-free survival has been longest in the estramustine phosphate adjuvant group for patients in Protocol 1,000 with nodal involvement. However, to date there has been no survival benefit to any adjuvant.

2) A higher recurrence rate is seen in patients with greater than 20% nodal metastases compared to those with less than 20% lymph node metastases. This effect is blunted in patients receiving adjuvant estramustine phosphate; whether this observation is due to the efficacy of the agent in large volume disease is unclear.

3) PFS has been better for D-1 (N+) patients in Protocol 1,000 if lymph node metastases were less than 20%. No such differences have been seen in Protocol 900.

4) For patients in Protocol 1,000 with greater than 20% lymph node involvement, the median progression-free survival has been significantly greater in the estramustine phosphate adjuvant group.

5) Lastly, there is as yet no apparent benefit of adjuvant treatment if nodal involvement is less than 20%.

All node-positive patients enrolled in Protocols 900 and 1,000 will be reviewed on a regular basis over the next several years to determine whether the results and trends presented here continue.

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REFERENCES

1. Murphy GP, Gibbons RP, Schmidt JD, Priore RL, Investigators of the National Prostatic Cancer Project: Prognostic significance of nodal status in stage D-1 prostate cancer. Abstract presented at Annual Meeting of the American Society of Clinical Oncologists, Atlanta, GA, May 17–19, 1988.
2. Schmidt JD, Gibbons RP, Bartolucci A, Murphy GP: Prognosis in stage D-1 prostate cancer relative to anatomic sites of nodal metastases (National Prostate Cancer Treatment Group). Cancer 64:1743–1746, 1989.
3. Kaplan EL, Meier P: Nonparametric estimates from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
4. Scott WW, Johnson DE, Schmidt JD, Gibbons RP, Prout GR, Joiner JR, Saroff J, Murphy GP: Chemotherapy of advanced prostate carcinoma with cyclophosphamide or 5-fluorouracil: results of first national randomized study. J Urol 114:909–911, 1975.
5. Murphy GP, Gibbons RP, Johnson DE, Loening SA, Prout GR, Schmidt JD, Bross DS, Chu TM, Gaeta JF, Saroff J, Scott WW: A comparison of estramustine phosphate and streptozotocin in patients with advanced prostatic carcinoma who have had extensive irradiation. J Urol 118:288–291, 1977.
6. Scott WW, Boyd HL: Combined hormone control therapy and radical prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate: a retrospective study based upon 25 years of experience. J Urol 101:86–92, 1969.
7. Cheng CWZ, Bergstralh EJ, Zincke H: Stage D1 prostate cancer. A nonrandomized comparison of conservative treatment options versus radical prostatectomy. Cancer 71:996–1004, 1993.
8. Kramer SA, Cline WA Jr, Farnham R, Carson CC, Cox EB, Hinshaw W, Paulson DF: Prognosis of patients with stage D-1 prostatic adenocarcinoma. J Urol 125: 817–819, 1981.
9. Olsson CA: Staging lymphadenectomy should be an antecedent to treatment in localized prostatic carcinoma. Urology 25(Suppl 2):4–6, 1985.
10. Prout GR Jr, Heaney JA, Griffin PP, Daly JJ, Shipley WU: Nodal involvement as a prognostic indicator in patients with prostatic carcinoma. J Urol 124:226–231, 1980.
11. Golimbu M, Provet J, Al-Askari S, Morales P: Radical prostatectomy for stage D-1 prostate cancer: prognostic variables and results of treatment. Urology 30:427–435, 1987.
12. Schmidt JD, McLaughlin AP III, Saltzstein SL, Garcia-Reyes R: Risk factors for the development of distant metastases in patients undergoing pelvic lymphadenectomy for prostatic cancer. Am J Surg 144:131–135, 1982.
13. Smith JA Jr, Middleton RG: Implications of volume of nodal metastasis in patients with adenocarcinoma of the prostate. J Urol 133:617–619, 1985.
14. Hartley-Asp B: Estramustine induced mitotic arrest in the two human prostatic carcinoma cell lines DU145 and PC-3. Prostate 5:93–100, 1984.
15. Eklöv S, Niksson S, Larson A, Björk P, Hartley-Asp B: Evidence for a non-estrogenic cytostatic effect of estramustine on human prostatic carcinoma cells in vivo. Prostate 20:43–50, 1992.