

SPECIAL ARTICLE

SURVIVAL AND QUALITY OF LIFE AMONG PATIENTS RECEIVING UNPROVEN AS COMPARED WITH CONVENTIONAL CANCER THERAPY

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Abstract *Background.* Cancer treatments without proved efficacy have achieved new levels of popularity, particularly among well-educated patients. The value of these therapies is vigorously debated.

Methods. We compared the length of survival and quality of life in patients who received treatment at a prominent unorthodox cancer clinic in addition to conventional treatment and in matched control patients from an academic cancer center who received only conventional treatment. All the patients had documented extensive malignant disease associated with a predicted median survival time of less than one year. The study sample consisted of 78 pairs of patients matched according to sex, race, age, diagnosis, and time from the diagnosis of metastatic

or recurrent disease, who were enrolled over a period of 3½ years. Periodic follow-up (approximately every two months) continued until death.

Results. There was no difference between the two patient groups in length of survival. Median survival for both groups was 15 months ($P = 0.22$; relative risk, 1.23; 95 percent confidence interval, 0.88 to 1.72). Quality-of-life scores were consistently better among conventionally treated patients from enrollment on.

Conclusions. For this sample of patients with extensive disease and for this particular unorthodox treatment regimen, conventional and unorthodox treatments produced similar results. (N Engl J Med 1991; 324: 1180-5.)

THE use of cancer treatments without proved benefit has become a major public health issue, with substantial numbers of patients deserting potentially curative conventional therapy in favor of unproved methods.^{1,2} The late Congressman Claude Pepper's Select Subcommittee on Quackery estimated that more than \$10 billion is spent annually on dubious methods of treating cancer.³ Recently, lobbyists for unproved treatments persuaded Congress to mandate a study to evaluate a particular unproved method.⁴

Through anecdotes and case reports, unorthodox practitioners and their patients and supporters claim success for their regimens in curing cancer and other illnesses. Given the lack of both controlled investigations and an understanding of the scientific method, the public is often drawn to these testimonials, which promise not only cure but also a better quality of life through the use of "non-toxic, natural" alternatives to the "cutting, burning, and poisoning"⁵ of conventional cancer care.

Toxicity is also an issue with unproved treatments. The few scientific investigations or reports of unorthodox cancer regimens include documentation of deaths resulting from colonic irrigation⁶ and coffee enemas,⁷ "detoxification" procedures that are central components of some therapies.⁸ Sensory neuropathy has also been reported in seven patients receiving high doses of pyridoxine hydrochloride (vitamin B₆).⁹ Other substances used in unorthodox regimens, although not evaluated in clinical trials, have been analyzed and reported to be worthless or harmful.¹⁰⁻¹⁷ The only clinical trials of unorthodox treatments in recent years have been studies of laetrile (amygdalin)^{18,19} and ascorbic acid (vitamin C),²⁰ in which investigators

found these products to be ineffective against advanced malignant disease. There is thus little in the way of convincing data concerning the clinical efficacy and toxicity of contemporary unproved cancer treatments, and even less information regarding the higher quality of life claimed to be associated with them.

This matched-cohort study of patients with end-stage cancer provides data on survival and quality of life among patients following an unproved regimen, as compared with patients receiving conventional care. Patients with cancer who were receiving the unproved treatment at the Livingston-Wheeler Medical Clinic in San Diego, California — which treats patients with an autogenous immune-enhancing vaccine, bacille Calmette-Guérin, vegetarian diets, and coffee enemas — were enrolled in the study with the full cooperation of the clinic.²¹ We selected this clinic because it uses a well-known and popular regimen, because its patients' histories were made available to us, and because physicians and other clinic staff wished to cooperate fully with the investigation.

We hypothesized that survival time would not differ between the two groups, on the basis of the assumption that the unproved remedy would be no more effective in patients with end-stage disease than conventional care, itself largely ineffective. A second hypothesis was that the quality of life of the patients receiving unproved therapy would be superior to that of the patients receiving conventional care. This hypothesis was based on the benefits that patients are thought to receive from various aspects of unorthodox therapy, especially its self-care components,^{1,22} and on the absence of the toxicity often associated with chemotherapy.

METHODS

Subjects

Patients treated at the University of Pennsylvania Cancer Center served as controls; case patients were treated at the Livingston-Wheeler Clinic. Eligibility criteria included the documentation of

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cancer by tissue biopsy, no previous diagnosis of cancer (other than nonmelanoma skin cancer), the absence of brain metastases at enrollment, an age of 21 years or more, awareness of the diagnosis, literacy, willingness to give informed consent, and (for the Livingston-Wheeler group) continued treatment with the main component of the unorthodox regimen, the autogenous vaccine, twice a week for at least one month, as prescribed.

Patients selected for study were those with diagnoses associated with extensive disease and a median estimated survival time of one year or less, with or without conventional therapy.²³⁻²⁶ The following diagnostic groups were included: Dukes' Stage D or recurrent unresectable colon or rectal cancer; metastatic, unresectable, or recurrent unresectable non-small-cell lung cancer; disseminated melanoma; and unresectable adenocarcinoma of the pancreas. For patients whose disease was not unresectable or metastatic at initial diagnosis (e.g., some patients with melanoma), the time of diagnosis was defined as the date of documented metastatic disease. This was done in accordance with eligibility requirements, and to enroll patients at similar stages of disease. Clinical homogeneity in the study sample at enrollment was thereby achieved.

Conventionally treated subjects were defined as patients who remained under the exclusive care of a conventional oncologist or other physician in a standard medical setting. Such patients were sought from daily lists of inpatients and outpatients scheduled to attend the hematology-oncology and radiation-therapy clinics at the Hospital of the University of Pennsylvania. After the patients' charts had been reviewed to verify the tissue-biopsy evidence of diagnosis, consecutive patients with eligible diagnoses were invited to participate in the study.

Patients treated with unproved methods were defined as those receiving treatment at the Livingston-Wheeler Clinic, regardless of whether they also received conventional care. The regimen at the clinic is based on Dr. Livingston-Wheeler's studies of a wide variety of cancer tissues, resulting in the putative discovery of a similar microorganism in all of them. Dr. Livingston-Wheeler reported that when provided with unlabeled tissue samples, she could identify the cancerous tissue by the presence or absence of the microorganism, which she identified as *Progenitor cryptocides*.^{27,28} The treatment regimen is based on the premise that it is necessary to produce immunity in the host in order to resist the infectious agent. To accomplish this goal, injections of bacille Calmette-Guérin and an autogenous immune-enhancing vaccine are given. The regimen also includes eliminating all animal products from the diet, in the belief that they may be infected by the microorganism; a strict vegetarian diet, 75 percent of it raw; and coffee enemas.²⁸ Patients from across the United States and abroad seek care at the Livingston-Wheeler Clinic, remaining there for approximately one week to receive the initial therapy and training in the application of the regimen at home.

The chemotherapy received by all but six of the study subjects consisted of standard agents; the six, all from the Hospital of the University of Pennsylvania, were treated with interleukin-2 or another experimental agent. Because these patients did not differ from the others in length of survival or demographic characteristics, they were included with the other patients treated at the Hospital of the University of Pennsylvania in our analyses.

Consecutive patients with eligible diagnoses who were attending the Livingston-Wheeler Clinic were asked to participate in the study. This was done by one of us, who worked initially at the Hospital of the University of Pennsylvania as part of the study and then at the Livingston-Wheeler Clinic until the study ended. The number of University of Pennsylvania ($n = 44$) and Livingston-Wheeler ($n = 37$) patients who were too ill to participate (24 percent and 27 percent, respectively) was approximately equal and did not differ demographically. On the basis of variables for which data could be collected, the study groups thus appeared to be representative of larger patient populations and free of sampling bias.

Consent forms, completed questionnaires, and the names and addresses of the patients' conventional physicians and hospitals were forwarded to us by the Livingston-Wheeler Clinic. A research assistant then contacted each patient's conventional physician and hospital to obtain copies of medical records to confirm study eligibility. Medical records were obtained for all study subjects.

Pairs of patients receiving conventional or unorthodox treatment were matched according to sex, race, age (<59 or ≥ 60 years), diagnosis, and date of metastatic or recurrent disease. Historical con-

trols were used for three patients. Matching according to these criteria was designed to reduce experimental variation. Both matched and unmatched analyses were performed, and their results are reported. Relative risks and 95 percent confidence intervals are given, and all P values reflect two-tailed tests unless otherwise noted.

Twenty of the Livingston-Wheeler patients could not be matched with University of Pennsylvania patients, and 65 University of Pennsylvania patients could not be matched with Livingston-Wheeler patients. These unmatched patients were not included in the study. A total of 78 matched, eligible pairs of patients made up the study sample (Table 1). Because of the difficulty of matching patients according to the study variables, enrollment took 3½ years.

Study Instruments

At enrollment only, all the patients undergoing conventional or unorthodox therapy gave informed consent and provided demographic information. Follow-up testing was performed every two months until the patient's death or the conclusion of the study. At enrollment and as part of each follow-up test, all the patients indicated their performance status according to the criteria of the Eastern Cooperative Oncology Group: capable of normal activities; symptomatic but ambulatory; bedridden <50 percent of the time; bedridden ≥ 50 percent of the time but not completely; or completely bedridden. Also at enrollment and as part of each follow-up test, quality of life was assessed with the Functional Living Index — Cancer, a 22-item self-report scale developed for repeated use by patients with cancer.²⁹ The index addresses functional issues but is not limited to functions so basic as to preclude obtaining a range of responses among subjects and over time in the same subject. The scale provides a single quality-of-life score based on indexes of perceived physical well-being, psychological state, sociability, effect on family members, and nausea, which had emerged as an independent factor during the development of the test.²⁹

Follow-up testing was conducted by telephone approximately every two months by research assistants who used an interview guide. Follow-up was complete for all patients until death or until poor clinical status just before death precluded responding to questions. Postenrollment data (Table 2) were incomplete for patients who died before the first two-month follow-up test (but who had been following the unproved regimen for the required minimum of one month). Patients undergoing unorthodox therapy received a detailed treatment-information form listing autogenous vaccines, vitamins, minerals, enemas, special diets, and other unconventional

Table 1. Demographic Characteristics of the Study Patients.*

CHARACTERISTIC	UNIVERSITY OF PENNSYLVANIA PATIENTS (N = 78)	LIVINGSTON-WHEELER PATIENTS (N = 78)
Median age (yr)	58	59
	number (percent)	
Sex		
Male	49 (63)	49 (63)
Female	29 (37)	29 (37)
Marital status		
Married	64 (84)	66 (85)
Other	12 (16)	12 (15)
Education		
≤High-school graduate	36 (49)	26 (34)
≥College graduate	37 (51)	51 (66)
Occupation		
Blue collar	23 (30)	17 (23)
White collar	35 (46)	31 (41)
Professional	18 (24)	27 (36)
Annual income		
<\$30,000	19 (34)	19 (26)
\$30,000-\$60,000	18 (33)	22 (30)
>\$60,000	18 (33)	32 (44)
Religion		
Protestant	24 (33)	39 (51)
Catholic	32 (44)	23 (30)
Other	17 (23)	15 (19)

*Data on all characteristics were not available for all patients.

Table 2. Clinical Characteristics of the Study Patients.*

CHARACTERISTIC	UNIVERSITY OF PENNSYLVANIA PATIENTS (N = 78)	LIVINGSTON-WHEELER PATIENTS (N = 78)
	number (percent)	
Performance status at enrollment		
Fully ambulatory	51 (69)	46 (59)
Symptomatic but ambulatory	20 (27)	25 (32)
Bedridden	3 (4)	7 (9)
Final performance status: ambulatory	52 (75)	42 (68)
Type or site of cancer		
Colon	31 (40)	31 (40)
Rectum	7 (9)	7 (9)
Lung	27 (35)	27 (35)
Pancreas	8 (10)	8 (10)
Melanoma	5 (6)	5 (6)
Chemotherapy		
Before enrollment	40 (52)	24 (31)
After enrollment	44 (64)	29 (47)
Radiation therapy		
Before enrollment	33 (43)	26 (34)
After enrollment	22 (32)	21 (34)
Surgery		
Before enrollment	55 (71)	54 (70)
After enrollment	22 (32)	23 (37)

*Data on all characteristics were not available for all patients. Pre-enrollment data on treatments received were incomplete because of inadequate information from the community hospitals that referred patients to the Hospital of the University of Pennsylvania and other tertiary care centers after initial diagnosis. Postenrollment data were available only for patients who lived until the first two-month follow-up.

and conventional therapies, with instructions to check those they had received since the previous test.

Information was obtained from both groups of patients about all conventional or unproved treatments they had received and about side effects, including nausea, vomiting, diarrhea, constipation, changes in appetite or weight, performance status, pain, dyspnea, cough, and comorbidity. In addition, patients were mailed the self-report quality-of-life scale.

RESULTS

Demographic and Clinical Findings

A total of 156 patients were enrolled in the study, half from the Hospital of the University of Pennsylvania and half from the Livingston-Wheeler Clinic. The Livingston-Wheeler patients came from 22 states. More (24 patients) lived in California than any other state, but 8 lived in Texas, 6 in New York, and 4 each in Illinois, New Jersey, and Pennsylvania (there were also 4 from Canada).

The patients ranged in age from 24 to 81 years, with a median age of 59. Most were married (84 percent), and most were well educated: 66 percent of the Livingston-Wheeler patients and 51 percent of the University of Pennsylvania patients were college graduates or had attended graduate school. More Livingston-Wheeler patients were in the highest income bracket, and more (77 vs. 70 percent) had white-collar or professional occupations. Unlike the University of Pennsylvania patients, Livingston-Wheeler patients were predominantly Protestant. These differences between the two groups of patients were not significant at $P < 0.05$, however. The Livingston-Wheeler patients

were all white. Because race was a matching factor, all the patients in the study were therefore white. The majority were men (63 percent of the sample). The demographic characteristics of the patients are shown in Table 1.

The Livingston-Wheeler patients had been given their diagnoses an average of 13.8 months before enrollment, and the University of Pennsylvania patients an average of 13.2 months before enrollment. Half the patients in each group had colorectal cancer, one third had non-small-cell lung cancer, 10 percent had pancreatic cancer, and 6 percent had melanoma. All of them had recurrent or metastatic disease, and most underwent surgery, chemotherapy, or radiation therapy before or after enrollment (Table 2).

Data on performance status indicated that 96 percent of the University of Pennsylvania patients and 91 percent of the Livingston-Wheeler patients were ambulatory at enrollment ($P = 0.22$), and 75 percent of the University of Pennsylvania patients and 68 percent of the Livingston-Wheeler patients were ambulatory as of the last telephone interview ($P = 0.33$) (Table 2). When data collection was complete, four patients (3 percent of the total sample) had survived for more than 36 months after diagnosis. Three were University of Pennsylvania patients who had survived for as long as 43 months. The longest survivor, a Livingston-Wheeler patient, was alive 45 months after the diagnosis of malignant disease.

Hypotheses and Analyses

The first hypothesis, based on the infrequency of clinical improvement in patients with advanced disease, was that there would be no difference in survival between patients receiving treatment at the Livingston-Wheeler Clinic and those receiving conventional care. Product-limit estimation was used to compute survival curves. Statistical comparisons of the curves with the Breslow, Mantel-Cox, and Tarone-Ware statistics were used to ascertain differences. For both Livingston-Wheeler and University of Pennsylvania patients, the median length of survival after the diagnosis or date of recurrent or metastatic disease was 15 months (Fig. 1) ($P = 0.5$ by the Breslow statistic, 0.2 by the Mantel-Cox statistic, and 0.4 by the Tarone-Ware statistic). Three statistics were used because each weights observations somewhat differently. The Breslow statistic assigns weight according to the number of patients at risk, the Tarone-Ware assigns weight according to the root of the number of patients at risk, and the Mantel-Cox weighs all equally.

Analyses of differences in survival according to each demographic and clinical characteristic (Tables 1 and 2) indicated that only sex was significantly related to survival ($P = 0.04$), with women living longer than men (median, 17 vs. 14 months). This is consistent with national data.³⁰ There were no statistically significant differences in survival either within or between groups according to whether chemotherapy, radiation therapy, or surgery (alone or in combination) was re-

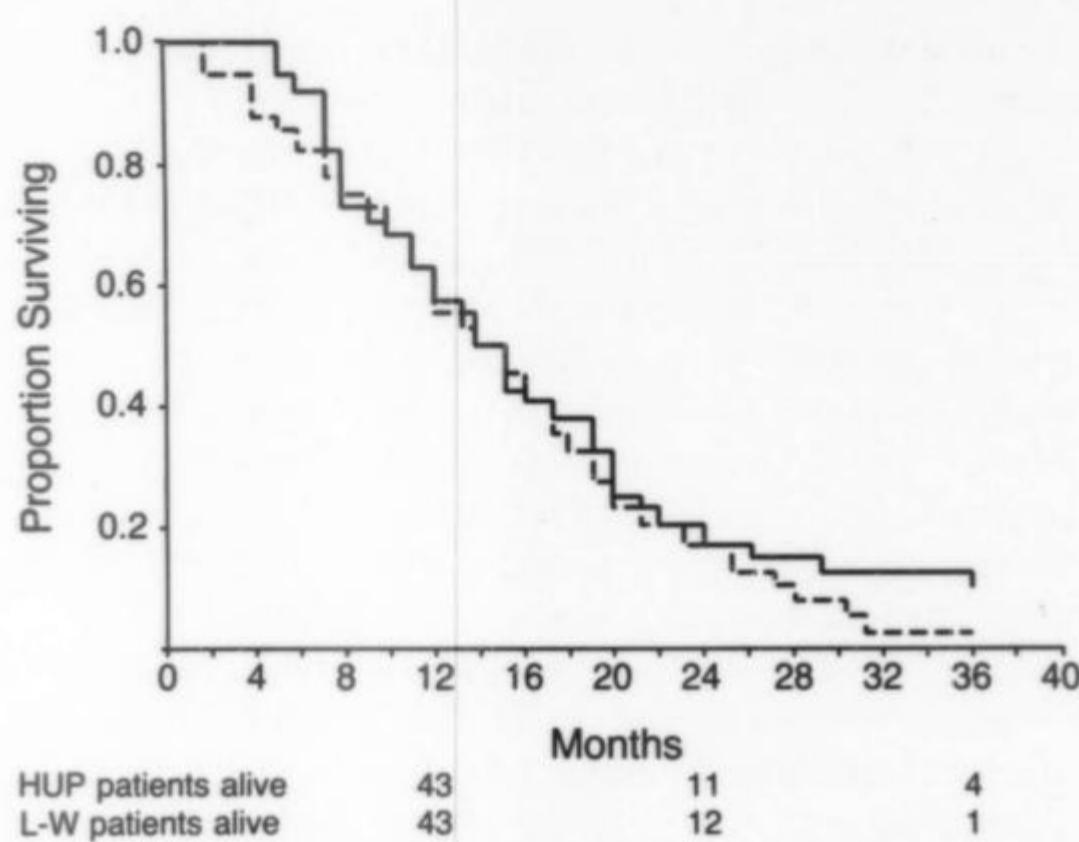


Figure 1. Kaplan-Meier Survival Curve for 78 Patients Treated for Cancer at the Livingston-Wheeler Clinic (L-W; Dashed Line) and 78 Matched Controls Treated at the Hospital of the University of Pennsylvania (HUP; Solid Line).

ceived before or after enrollment. That is, no differences emerged between patient groups when they were stratified according to receipt of chemotherapy or radiation therapy, either individually or in combination, or according to different types of chemotherapy. As would be expected, the patients in both groups who underwent surgery lived longer than those who did not undergo surgery. However, there was no difference in length of survival between Livingston-Wheeler and University of Pennsylvania patients when stratified according to whether they had had surgery.

The only potentially confounding variable among those studied was performance status, identified through variable-by-variable analysis. Consequently, in order to account for performance status as a covariate, all patient pairs whose performance status differed by two or more categories were removed from the analysis, and differences in survival were reexamined without them. Again, there were no significant differences ($P = 0.9$ by the Breslow statistic, 0.7 by the Mantel-Cox statistic, and 0.9 by the Tarone-Ware statistic). In addition, matched analyses were performed for pairs of deceased patients ($P = 0.6$), and survival analyses³¹ were conducted for matched patients ($P = 0.5$). Finally, a Cox regression model was used to evaluate the following variables: age, sex, income level, performance status, treatment (unorthodox vs. conventional), marital status, education, initial Functional Living Index scores, and chemotherapy before and after enrollment. Only sex approached significance ($P = 0.06$; relative risk, 1.39; 95 percent confidence interval, 1.00 to 1.97), thereby confirming the previously noted result.

The second research hypothesis was that quality of life would be better among Livingston-Wheeler patients than among University of Pennsylvania patients. This hypothesis was tested with repeated-measures analysis of variance. The University of Pennsylvania patients had a significantly better quality of life

at all times ($P = 0.002$), including enrollment. Furthermore, the differences in quality of life over time were also significant ($P < 0.001$) (Fig. 2). Finally, there were no interaction effects ($P = 0.92$), meaning that quality of life deteriorated at an equal rate in the two patient groups.

Chemotherapy had no effect on quality of life. Patients in both groups reported adverse effects regardless of whether they received chemotherapy. More Livingston-Wheeler patients than University of Pennsylvania patients reported adverse effects. Appetite problems were noted by 79 percent of the Livingston-Wheeler patients and 71 percent of the University of Pennsylvania patients receiving chemotherapy, and by 76 percent of the Livingston-Wheeler patients and 52 percent of the University of Pennsylvania patients who did not receive chemotherapy after enrollment. Pain was reported by 72 percent of the Livingston-Wheeler patients and 54 percent of the University of Pennsylvania patients who received chemotherapy, and by 54 and 56 percent, respectively, of those who did not. Breathing difficulties were noted by 76 percent of the Livingston-Wheeler patients and 61 percent of the University of Pennsylvania patients who received chemotherapy, and by 45 and 64 percent, respectively, of those who did not. Age and other demographic characteristics were not related to quality of life.

DISCUSSION

There are a number of methodologic flaws intrinsic to this investigation. Because random assignment was not an option, patients were self-selected in their use of conventional or unorthodox treatment. The potential implications of self-selection bias remain a matter of speculation, awaiting the clarification that can

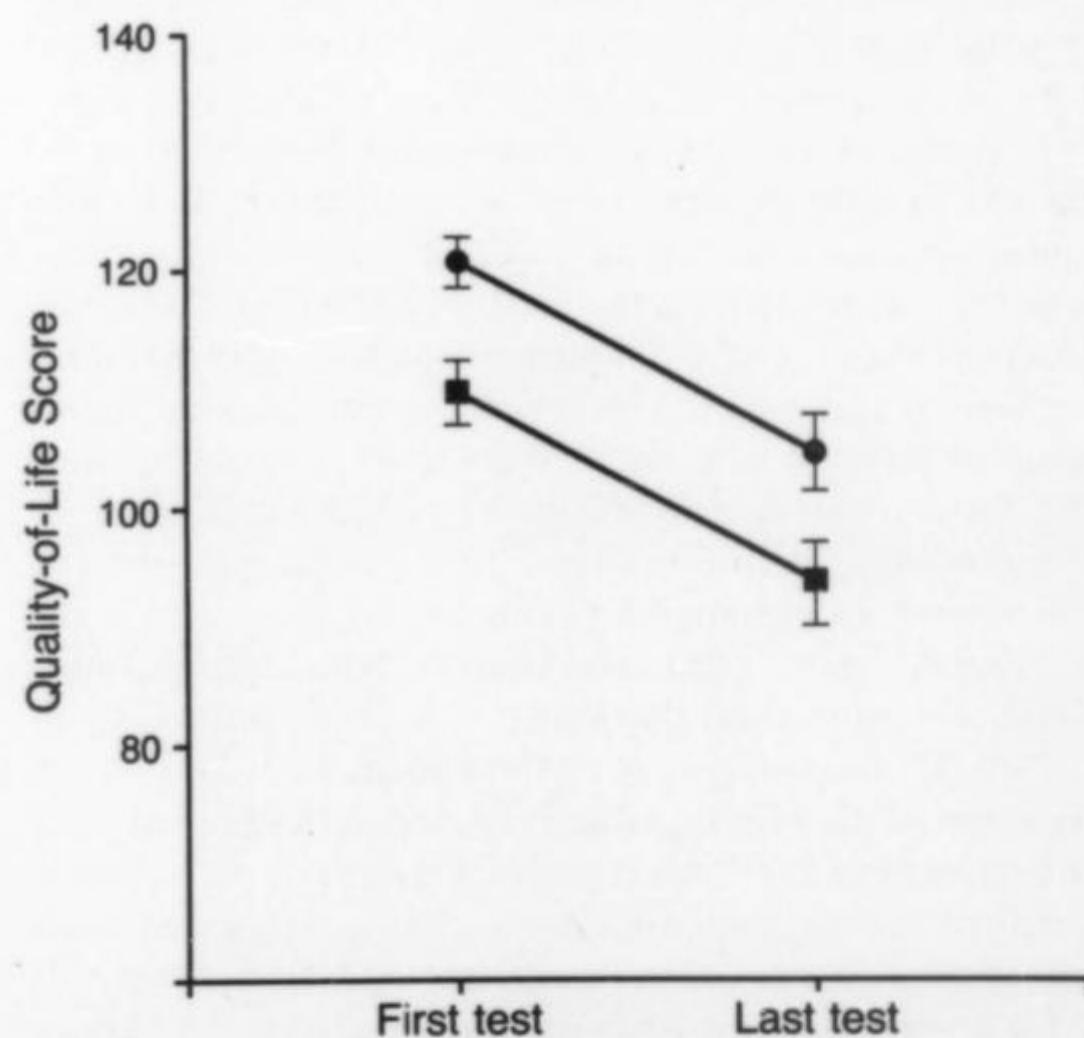


Figure 2. Mean (\pm SE) Quality-of-Life Scores over Time for Patients Treated at the Livingston-Wheeler Clinic (Squares) or at the Hospital of the University of Pennsylvania (Circles).

come only with randomized trials. Furthermore, the nature of telephone interviews precluded blinding research assistants to knowledge of the patients' sources of treatment, so interviewer bias cannot be ruled out. In addition, the use of eligibility criteria that restricted the sample to patients with extensive disease, although it provided a rigorous test of treatment efficacy at that clinical stage, did not permit an evaluation of efficacy in patients with less extensive disease, in whom treatment has more opportunity to succeed. Finally, one of the outcomes — quality of life — was different at base line in the two groups.

The principal finding of this study was that length of survival did not differ in the two groups of patients, indicating that the conventional and unproved treatments studied were similar in efficacy. This study explored only one unorthodox therapy, the regimen of the Livingston-Wheeler Clinic, and it involved only patients with diagnoses and stages of disease for which there is no effective conventional treatment. Therefore, the results cannot be generalized to patients with less advanced stages of disease or to other treatment regimens. With regard to clinically similar patients, however, our results suggest the likely futility of treatment per se, and the importance of having no-treatment arms in analogous clinical trials.

The actions of the Livingston-Wheeler patients seem consistent with the widespread and ongoing shift toward self-care and the active involvement of patients in medical decisions in the United States. Books, pamphlets, and audiovisual programs about various illnesses and treatments are readily available from national groups and organizations, including the National Cancer Institute and the American Cancer Society, to inform patients and to encourage their participation in care.

As patients and the public have become increasingly educated, dissatisfaction with conventional care for cancer has grown. The toxic effects of chemotherapy, the absence of new and markedly improved treatments despite decades of effort, and the lack of substantive improvement in rates of cure for the major cancers all contribute to the dissatisfaction. Concerns such as these lead substantial numbers of physicians as well as patients to reject conventional cancer medicine in favor of unproved alternatives. Simultaneously, they are drawn to the perceived benefits of unorthodox care, including the hope of prolonged survival, cure, and an enhanced quality of life.^{1,2}

Today, it is primarily better educated patients who seek unproved therapies.^{1,2} A confirmatory trend ($P<0.05$, one-tailed) is evidenced in our data — 66 percent of the Livingston-Wheeler patients, but only 51 percent of the University of Pennsylvania patients, had college or graduate degrees. However, as patients in other demographic strata become knowledgeable and assertive about their own medical care and treatment, as younger people who are acculturated to being informed and active become patients, and as the absence of new and more effective conventional treat-

ments continues, a trend toward increased selection of unproved therapies seems likely.

As long as there are no effective treatments for patients with advanced diseases such as those studied here, maintaining or at least not harming the quality of life remains all that can be offered. For that reason, quality of life, along with length of survival, was a major outcome variable in this study. It had been hypothesized that Livingston-Wheeler patients would have a better quality of life on the basis of the primary assumption that they would be free of the toxicity often associated with conventional therapy.

Some patients in both groups received conventional treatment after enrollment (Table 2), and quality of life was significantly and inversely related to appetite difficulties and pain among the Livingston-Wheeler patients and to nausea and pain among the University of Pennsylvania patients. No significant relation emerged in either group, however, between chemotherapy and quality of life. It is of interest that both the University of Pennsylvania and the Livingston-Wheeler patients had adverse effects, regardless of whether they received chemotherapy. In the absence of chemotherapy, it is likely that disease factors contributed to the symptoms in both groups. Because more Livingston-Wheeler patients than University of Pennsylvania patients reported adverse effects, it may be assumed that the Livingston-Wheeler regimen also contributed to the symptoms reported.

These results also indicate that treatment and its side effects alone do not determine quality of life. Rather, they serve as only one influencing factor. This is consistent with the basic concept of quality of life, which holds that it comprises several major components of existence.²⁹ It may be that poorer quality of life contributes to the decision to seek unproved therapy, or that patients who are so inclined have higher expectations of improvement and therefore greater disillusionment if it fails to achieve anticipated benefits.

Despite substantial adverse effects in both groups, quality of life was better in the patients undergoing conventional care, whose quality of life was also better at enrollment. It is possible that quality of life is influenced in part by the care received in a particular setting, and that other medical environments would further enhance (or diminish) quality of life. Nevertheless, this study refutes the assumption that unproved therapies necessarily enhance the quality of life.

Our findings suggest that conventional therapy for the kinds of diseases studied here should be measured against a no-treatment alternative involving only palliative care. This study also illustrates the feasibility of conducting an investigation of patients receiving an unproved treatment for cancer, given the cooperation of the unorthodox clinic or practitioner. Substantial numbers of patients and physicians who are involved with various unproved methods argue and lobby for acceptance. Some of the regimens they promote, like that studied here, may warrant appropriate investigation.

We are indebted to Virginia Livingston-Wheeler, M.D., who died shortly after the completion of this study, for her full cooperation with this investigation and for encouraging her patients and staff to participate; she worked tirelessly to allow an unbiased evaluation of her regimen. We are also indebted to the many physicians who provided information, materials, or access to their patients, and especially to the patients, most of them now deceased, and their families, whose interest and efforts made this study possible; to the more than 40 students, research assistants, and faculty members who worked on various phases of this study and who contributed so importantly to it, particularly Barbara Doyle, R.N., M.S., Beth Frederick, John H. Glick, M.D., W. Thomas London, M.D., Rajesh Singal, and Ellen Zaleta; and to Priyamvada Chandra, Jennifer Chou, and Annette M. Martinez for assistance in the preparation of the manuscript and other help.

REFERENCES

1. Cassileth BR, Lusk EJ, Strouse TB, Bodenheimer BJ. Contemporary unorthodox treatments in cancer medicine: a study of patients, treatments, and practitioners. *Ann Intern Med* 1984; 101:105-12.
2. Cassileth BR. Unorthodox cancer medicine. *Cancer Invest* 1986; 4:591-8.
3. House Select Committee on Aging. Quackery: a \$10 billion scandal. 98th Congress, second session, May 31, 1984. Washington, D.C.: Government Printing Office, 1984 (SUDOC no. 98-435.)
4. Office of Technology Assessment. Unconventional cancer treatments. Washington, D.C.: Government Printing Office, 1990. (OTA publication no. OTA-H-405.)
5. Deverell D. How I healed my cancer holistically and discovered the cancer cover-up. USA: Dore Deverell, 1978.
6. Istre GR, Kreiss K, Hopkins RS, et al. An outbreak of amebiasis spread by colonic irrigation at a chiropractic clinic. *N Engl J Med* 1982; 307:339-42.
7. Eisele JW, Reay DT. Deaths related to coffee enemas. *JAMA* 1980; 244:1608-9.
8. Gerson M. A cancer therapy: results of fifty cases. Del Mar, Calif.: Totality Books, 1977.
9. Schaumburg H, Kaplan J, Windebank A, et al. Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Engl J Med* 1983; 309:445-8.
10. Hindmarsh W, LeGatt DF. Mexican drug therapy. *Clin Toxicol* 1980; 17:85-99.
11. Herbert V. Nutrition cultism: facts and fictions. Philadelphia: George F. Stickley, 1980.
12. American Cancer Society. Unproven methods of cancer management: anti-neoplastons. *CA* 1983; 33:57-9.
13. *Idem*. Unproven methods of cancer management: Haritan Alivizatos, M.D. ("Greek Cancer Cure"). *CA* 1983; 33:252-4.
14. *Idem*. Unproven methods of cancer management: immuno-augmentative therapy. *CA* 1984; 34:232-7.
15. Bowman BB, Kushner RF, Dawson SC, Levin B. Macrobiotic diets for cancer treatment and prevention. *J Clin Oncol* 1984; 2:702-11.
16. DiPalma JR, McMichael R. Assessing the value of meganutrients in disease. *Bull N Y Acad Med* 1982; 58:254-62.
17. Curt GA, Katterhagen G, Mahaney FX Jr. Immunoaugmentative therapy: a primer on the perils of unproved treatments. *JAMA* 1986; 255:505-7.
18. Moertel CG, Ames MM, Kovach JS, Moyer TP, Rubin JR, Tinker JH. A pharmacologic and toxicological study of amygdalin. *JAMA* 1981; 245:591-4.
19. Moertel CG, Fleming TR, Rubin J, et al. A clinical trial of amygdalin (Laetrile) in the treatment of human cancer. *N Engl J Med* 1982; 306:201-6.
20. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy: a randomized double-blind comparison. *N Engl J Med* 1985; 312:137-41.
21. Wheeler VL, Wheeler OW. Compendium: the microbiology of cancer. San Diego, Calif.: Livingston-Wheeler Medical Clinic, 1980.
22. Cassileth BR, Lusk EJ, Walsh WP, Doyle B, Maier M. The satisfaction and psychosocial status of patients during treatment for cancer. *J Psychosoc Oncol* 1989; 7(4):47-57.
23. Portlock CS, Goffinet DR. Manual of clinical problems in oncology: with annotated key references. Boston: Little, Brown, 1980:168.
24. Minna JD, Higgins GA, Glatstein EJ. Cancer of the lung. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 2nd ed. Vol. 1. Philadelphia: J.B. Lippincott, 1985:507-97.
25. Mastrangelo MJ, Baker AR, Katz HR. Cutaneous melanoma. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 2nd ed. Vol. 2. Philadelphia: J.B. Lippincott, 1985:1371-422.
26. Sindelar WF, Kinsella TJ, Mayer RJ. Cancer of the pancreas. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 2nd ed. Vol. 1. Philadelphia: J.B. Lippincott, 1985:691-739.
27. Wuerthele-Caspe V, Brodkin E, Mermod C. Etiology of scleroderma. *J Med Soc N J* 1947; 44:256-9.
28. Livingston-Wheeler V, Addeo EG. *The conquest of cancer*. New York: Franklin Watts, 1984.
29. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: the Functional Living Index — Cancer: development and validation. *J Clin Oncol* 1984; 2:472-83.
30. Myers MH, Ries LA. Cancer patient survival rates: SEER program results for 10 years of follow-up. *CA* 1989; 39:21-32.
31. O'Brien PC, Fleming TR. A paired Prentice-Wilcoxon test for censored paired data. *Biometrics* 1987; 43:169-80.