Effect of Warfarin Anticoagulation on Survival in Carcinoma of the Lung, Colon, Head and Neck, and Prostate

Final Report of VA Cooperative Study #75

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VA Cooperative Study #75 was established to test in a controlled, randomized trial the hypothesis that warfarin anticoagulation would favorably affect the course of certain types of malignancy. No differences in survival were observed between warfarin-treated and control groups for advanced non-small cell lung, colorectal, head and neck and prostate cancers. However, warfarin therapy was associated with a significant prolongation in the time to first evidence of disease progression ($P = 0.016$) and a significant improvement in survival ($P = 0.018$) for patients with small cell carcinoma of the lung, including the subgroup of patients with disseminated disease at the time of randomization ($P = 0.013$). A trend toward improved survival with warfarin treatment was observed for the few patients admitted to this study with non-small cell lung cancer who had minimal disease at randomization. These results suggest that warfarin, as a single anticoagulant agent, may favorably modify the course of some, but not all, types of human malignancy, among which is small cell carcinoma of the lung. Further trials of warfarin may be indicated in patients with limited disease who have cell types that failed to respond when advanced disease was present.

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IN APRIL 1976, a controlled randomized therapeutic trial was initiated in patients with carcinoma of the lung, colon, prostate, and head and neck. The purpose of this study was to determine the effect of warfarin anticoagulation on certain predetermined response criteria. The rationale and experimental design of this study have been presented previously.[1] The results obtained in the subgroup of patients with small cell carcinoma of the lung (SCCL) admitted to this study have also been reported.[2] The concept that served as the basis for this study was that neoplastic cells in certain forms of cancer are capable of interacting with the blood coagulation mechanism and that this interaction allows the tumor cells to modify their local environment in a manner that is conducive to their growth and spread.[3]

This article reports the effects of warfarin on tumor responses and longevity in patients with tumor types under investigation. Other data from this study, including that on warfarin toxicity, will be reported separately.

Methods

The experimental design of this randomized, controlled trial of warfarin and a description of the tumor categories under investigation, exclusion criteria and standard therapy (chemotherapy, radiation therapy) given were presented previously.[1] Screening procedures were employed at participating hospitals in order to gather certain data on patients with tumor types of interest but who were not admitted to this study. Thus, information was ob-

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TABLE 1. Accrual to VA Cooperative Study #75

	Total	Warfarin-treated	Control
1. *Lung:* limited disease: all cell types except small cell, initially inoperable or recurrent following previous operation but disease limited to one hemithorax. The ipsilateral scalene nodes may be involved and the mediastium may be involved bilaterally but there will be no pulmonary parenchymal or pleural disease on the contralateral side.	64	31	33
2. *Lung:* disseminated disease: all cell types except small cell.	130	65	65
3. *Lung:* small cell carcinoma	50	25	25
4. *Colorectal:* adenocarcinoma, disseminated or locally recurrent disease.	68	34	34
5. *Prostate:* adenocarcinoma, with x-ray or bone scan evidence of disseminated disease.	24	14	10
6. *Head and neck:* epidermoid carcinoma, recurrent or progressive disease subsequent to adequate primary treatment. (Tumors of the lip and salivary gland are excluded.)	41	20	21
7. *Lung:* all cell types except small cell, following resection in which a "curative" procedure was used; no evidence of disseminated disease.	16	7	9
8. *Colorectal:* adenocarcinoma, Duke's C (penetration through serosa and/or involvement of regional nodes) following resection in which a "curative" resection was used, i.e., resection of the lesion and associated mesentery.	13	5	8
9. *Lung:* all cell types except small cell, following "curative" radiation therapy; no evidence of disseminated disease.	25	14	11
Total	431	215	216

tained on the reasons why patients failed to enter this study (to be reported in detail separately) and comparison of admitted *versus* excluded patients was permitted. Patients were admitted to this study from 13 different VA Medical Centers over a four year period and were followed for an additional 12 months. The cutoff date for data presented here was March 4, 1982. Accrual according to tumor category is presented in Table 1. Patients admitted to this study were subjected to computer randomization by hospital, performance status and tumor category to receive standard therapy either with or without warfarin anticoagulation.[1]

The effect of warfarin treatment on a number of parameters of interest was evaluated. Results were compared for all patients originally randomized to the study. The results were also analyzed separately after exclusion of patients who did not meet predetermined criteria for evaluability.[1] Patients were excluded if they did not receive at least one course of standard treatment or did not survive at least 2 weeks following randomization. In addition, patients randomized to receive warfarin were excluded if they did not receive at least 2 weeks of anticoagulant therapy following randomization. Application of these criteria resulted in exclusion of 57 patients (13% of the total).

Tumor responses evaluated included complete remission, partial remission, no change, or disease progression.[1] A complete remission was defined as complete disappearance of all signs and symptoms referable to the malignancy. A partial remission was defined as a reduction of 50% or more in the product(s) of perpendicular diameters of measured lesions on two successive visits with appearance of no new lesions. No change in the extent of disease was defined as an increase or decrease in the product(s) of perpendicular diameters of measured lesions of less than 50% with the appearance of no new lesions. Disease progression was defined as an increase of more than 50% in the product(s) of perpendicular diameters of measured lesions, the appearance of new lesions, or progression of other abnormal clinical or laboratory determinations indicative of disease progressions. Determination of disease progression or remission was made with reference to the extent of disease present at the time of randomization.

Longevity was defined as the interval between randomization and death. Survival curves were computed according to the method of Kaplan and Meier.[4] The modification of the Wilcoxon test by Gehan[5] was used to test for statistical significance between the survival curves for the warfarin-treated and control groups. The χ^2 test was used to compare qualitative characteristics between the warfarin and control groups, while the two-sample t test was used to compare quantitative characteristics between the two groups. All statistical tests used were two-sided.

Results

A total of 431 patients were admitted to this study between April 1976 and May 1980. As of the follow-up conclusion date for this report (March 4, 1982), 5 (1.2%) of the 431 patients were lost to follow-up. Only 13 patients were entered to this study who had had resection with curative intent for Duke's C carcinoma of the colon.

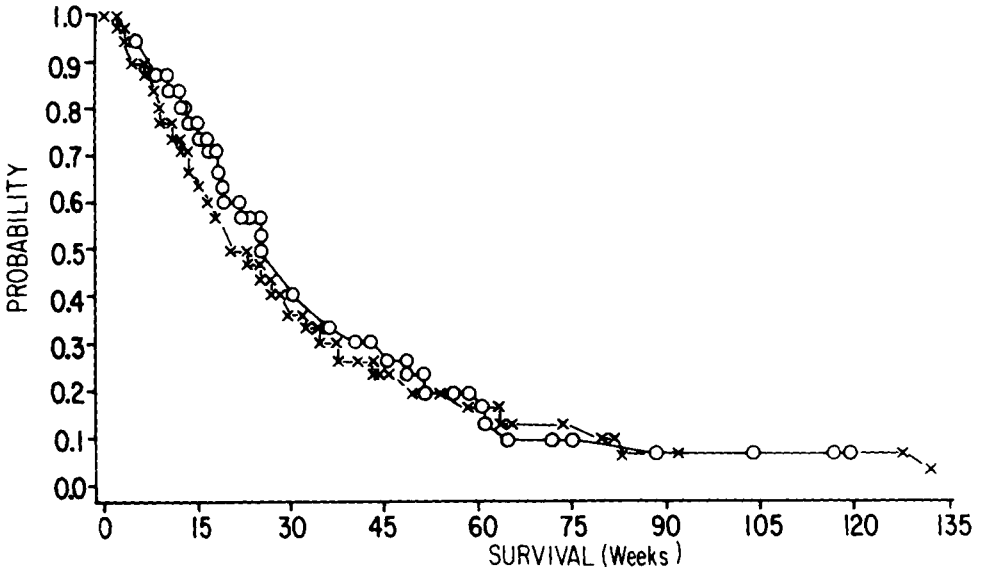

FIG. 1. Comparison of survival for 96 warfarin-treated (×) *versus* 98 control (O) patients with advanced non-small cell lung cancer entered to tumor categories 1 and 2 combined (Table 1). The median survival was 21.4 weeks for warfarin-treated and 24.6 weeks for control patients (P = 0.42).

Since no conclusions could be reached for this category, these patients were omitted from this analysis. Thus, results obtained in the remaining 418 patients are reported here.

The number of cases admitted to each of the tumor categories is presented in Table 1. Of the 431 patients that are the subject of this report, 377 have died as of October 1, 1981. A total of 189 of these patients were randomized to the warfarin-treated group and 188 patients to the control group. An attempt was made to detect differences between these two treatment groups for a number of parameters evaluated at the time of randomization. Equivalence was found between the two treatment groups for the mean age, body weight, height, body surface area, sex, race, performance status, prior treatment, interval from original diagnosis to randomization, alkaline phosphatase determination, leukocyte count, platelet count, and prothrombin time. For patients with advanced colorectal cancer, there was no difference between treatment groups in the incidence of hepatic involvement at randomization as determined by the results of radioisotope liver scans as well as plasma alkaline phosphatase determinations.

The mean prothrombin time (average in all determinations) for warfarin-treated patients was 17.6 sec and for control patients 11.6 sec (P = 0.0001). For warfarin-treated patients, the mean duration of warfarin administration (time of randomization to last warfarin dose) was 26.4 weeks and ranged from a low of 8.2 weeks for patients with head and neck cancer to a high of 85.9 weeks for patients with non-small cell lung cancer following resection. The mean duration of warfarin administration was 64.9% of the total follow-up interval. The mean warfarin dose was 4.90 mg/day.

The effect of warfarin treatment on survival for all patients admitted to this study is presented in Figures 1 through 6. For purposes of this report, patients in categories 1 and 2 were combined, as were patients in categories 7 and 9. No differences in survival were observed between treatment groups for patients with advanced non-small cell lung, colorectal, prostatic, or head and neck cancer. Likewise, no differences in survival were observed for patients in the non-small cell lung cancer group upon further subdivision into squamous cell, large cell and adencarcinoma groups. A trend toward improved survival for warfarin-treated patients was observed for patients with non-small cell lung cancer following surgical resection or following potentially curative radiation therapy (strata 7 and 9, Fig. 6). By contrast, a significant improvement in survival was observed for patients with small cell carcinoma of the lung (P = 0.018, Fig. 2). Of the 50 patients with small cell lung cancer, 23 (12 warfarin-treated and 11 control) had evidence of disseminated disease at the time of randomization. Warfarin-treated patients within this subgroup also manifested a significant improvement in survival in comparison to control patients (P = 0.013). There were no differences between treatment groups for any tumor category in the incidence of complete or partial remissions, median length of remission, or incidence of disease progression.[1] The median time to first evidence of disease progression was the same between treatment groups for all tumor categories except small cell lung cancer. Warfarin-treated patients with small cell lung cancer had a significantly increased time to disease

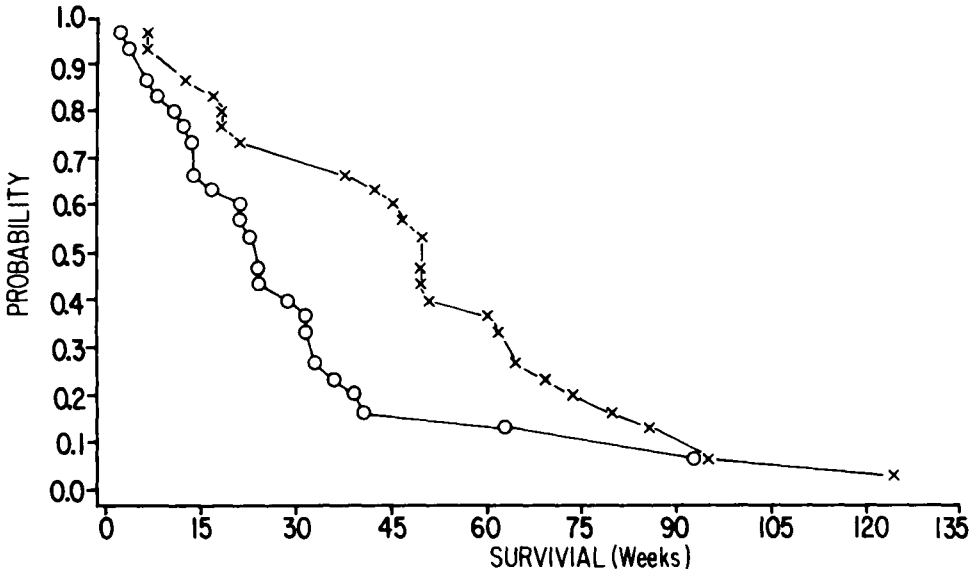

FIG. 2. Comparison of survival for 25 warfarin-treated (×) *versus* 25 control (O) patients with small cell carcinoma of the lung admitted to tumor category 3 (Table 1). The median survival was 49.5 weeks for warfarin-treated and 23.0 weeks for control patients ($P = 0.018$).

progression in comparison to control patients ($P = 0.016$). All of the above results were obtained from analysis of data from all patients entered to the study. The results were the same when calculations were made following exclusion of "ineligible" patients.

Autopsies were performed on 76 patients admitted to this study. Records were available for review of 71 of these (35 warfarin-treated and 36 control). Metastasis to a total of 30 different sites was analyzed. The control group had more metastases than the warfarin-treated group for 12 sites and fewer metastases for 14 sites. The incidence was the same for four sites. A comparison of warfarin-treated and control groups for the incidence of involvement of the seven most common sites of metastasis is presented in Table 2. No significant difference in the distribution of disease was observed between treatment groups, although the difference approached significance ($P = 0.069$) for liver metastasis.

An attempt was made to detect differences between patients with small cell carcinoma of the lung, that apparently responded to warfarin, and patients with other tumor types, that apparently did not respond to warfarin, based on analysis of all data available at the time of entry to the study. The intention was to search for differences that might provide insight into possible explanations for variation between tumor types in responsiveness to warfarin. In comparison to patients with other tumor types, patients with small cell lung cancer were found to have

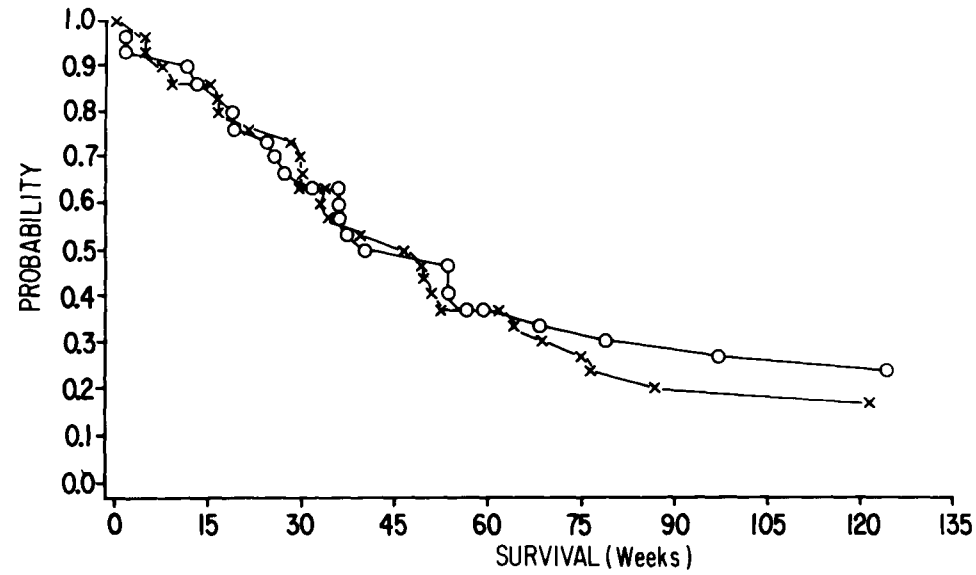

FIG. 3. Comparison of survival for 34 warfarin-treated (×) *versus* 34 control (O) patients with advanced colorectal cancer admitted to tumor category 4 (Table 1). The median survival was 47.0 weeks for warfarin-treated and 41.0 weeks for control patients ($P = 0.79$).

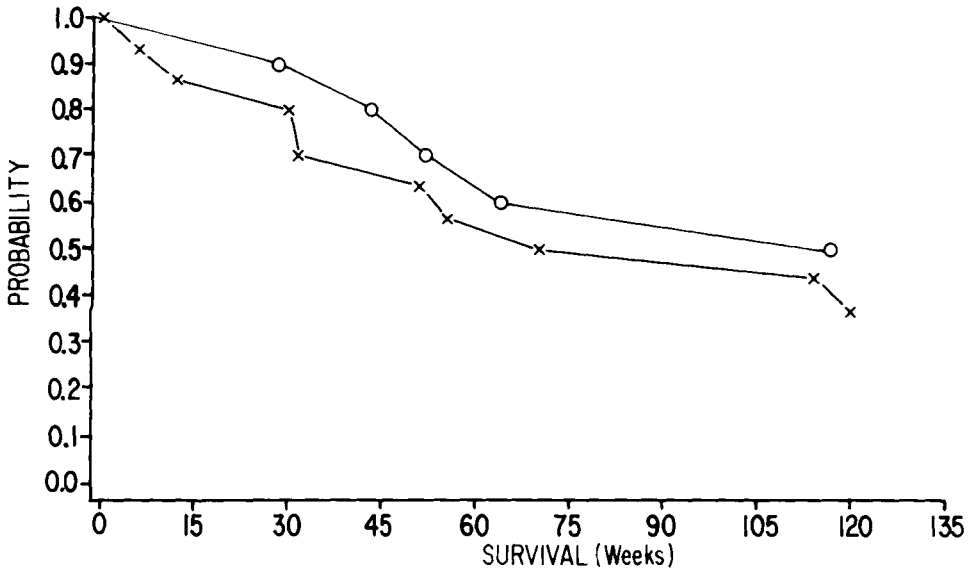

FIG. 4. Comparison of survival for 14 warfarin-treated (×) *versus* 10 control (○) patients with advanced prostate cancer admitted to tumor category 5 (Table 1). The median survival was 69.9 weeks for warfarin-treated and 116.6 weeks for control patients (P = 0.45).

a shorter mean interval between original diagnosis and a randomization (P = 0.000), a reduced incidence of prior surgery (P = 0.016), and a greater incidence of prior radiation therapy (P = 0.002). However, no insights were forthcoming that might explain differences in warfarin responsiveness.

Discussion

The anticoagulant approach to the containment of malignancy is based on evidence obtained in studies of experimental tumor systems.[1,3] This evidence suggests that either anticoagulants (such as warfarin) or platelet antagonists reduce tumor dissemination in different experimental models.[1,3,7] The relevance of this approach to human malignancy is uncertain. However, preliminary evidence suggests that it might indeed have merit.[6] Particularly promising results have been reported for warfarin in breast cancer and lymphoma.[8-10]

Warfarin was selected for this controlled, randomized trial because physicians are generally familiar with its use; the mechanism of its anti-coagulant effect is reasonably understood; it can be given on an outpatient basis to provide stable, long-term anticoagulation; complicance with treatment can be objectively assessed by means of laboratory tests; it is, perhaps, the most consistently effective anti-thrombotic drug in experimental malignancies;[11] and because of preliminary evidence for a favorable

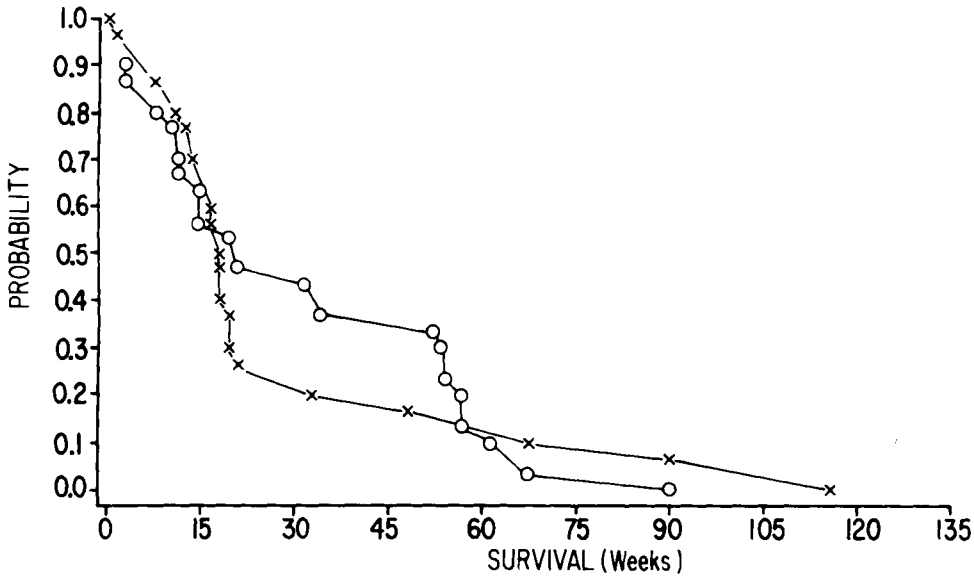

FIG. 5. Comparison of survival for 20 warfarin-treated (×) *versus* 21 control (○) patients with advanced head and neck cancer admitted to tumor category 6 (Table 1). The median survival was 18.0 weeks for warfarin-treated and 20.7 weeks for control patients (P = 0.66).

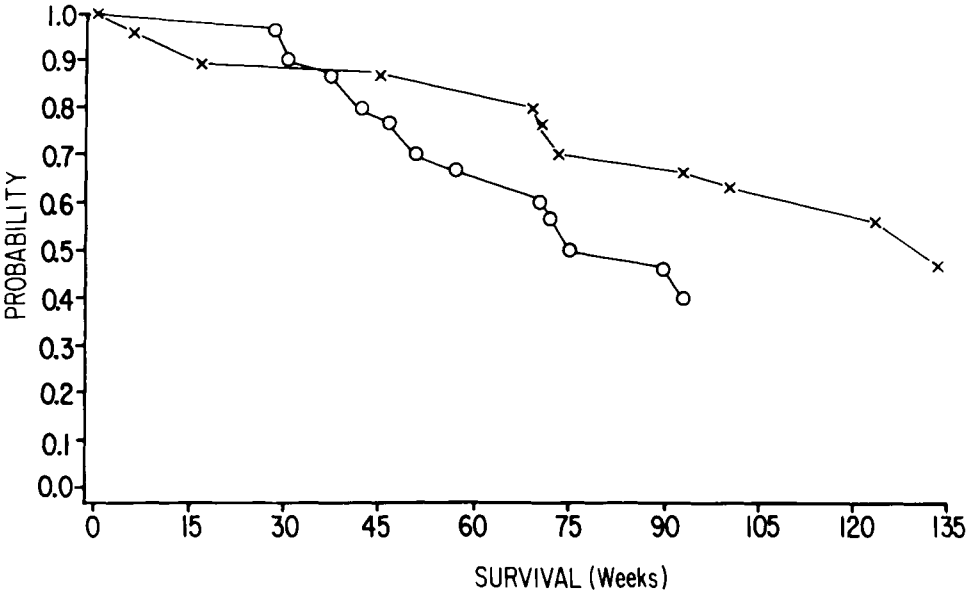

FIG. 6. Comparison of survival for 21 warfarin-treated (×) *versus* 20 control (○) patients who had no evidence of non-small cell carcinoma of the lung at the time of randomization following potentially curative surgical resection or radiation therapy. The data presented are for patients admitted to tumor categories 7 and 9 combined (Table 1). The median survival was 129.7 weeks for warfarin-treated and 75.3 weeks for control patients ($P = 0.20$).

effect in human malignancy.[6,8-10] While the tumor types included in the current study were not necessarily the type in which one would have anticipated a response, these were the types available to the study group, and these had not, in fact, been studied in a controlled fashion.

The mechanism by which warfarin limits tumor spread is not fully defined.[2] It is likely, however, that warfarin causes a reduction in the coagulant activity of tumor cells that is required for induction of local fibrin formation necessary for metastatic seeding.[11,12] Should this be true, one might predict that this drug would manifest its greatest effect when given to patients with minimal disease, for example, following surgical resection. Our observation that warfarin treatment was not associated with an increased incidence of remissions and of a trend toward improved survival in patients with non-small cell carcinoma of the lung who had no evidence of macroscopic disease at the time of randomization is consistent with this hypothesis. However, the value of our data is limited not only by the fact that relatively few such patients were available to our group but also by the fact that study rules permitted entry of patients with no evidence of disease as long as 3 months following initial surgery or radiotherapy. Conceivably a greater difference between warfarin-treated and control patients might have been observed had the drug been started earlier in the course of the disease.

TABLE 2. Location of the Seven Most Common Sites of Metastatic Disease Found at Autopsy in Thirty-five Warfarin-treated and Thirty-six Control Patients

	No. with metastases	
Metastatic site	Warfarin-treated	Control
Lung	19	22
Liver	16	24
Lymph nodes	20	19
Bone	18	16
Adrenal gland	13	15
Kidneys	8	12
Brain	5	11

The beneficial effect of warfarin in SCCL was unexpected. A delay in disease progression was accompanied by a significant prolongation of survival for this tumor type.[2] This benefit was particularly evident in the subgroup of patients in this category who had disseminated disease at the time of randomization. Should these results be confirmed, it may be that SCCL is biologically different from the other tumor types tested in that it is particularly dependent on the coagulation mechanism for its sustenance.

Our findings indicate that an acceptable level of anticoagulation can be achieved on a sustained basis in patients with cancer. Thus, further trials of this drug in patients with malignancy would appear to be feasible. Should our favorable results in SCCL be confirmed, it may be that other tumor types will be identified that are also responsive to warfarin. Unfortunately, there is at present no means by which responsiveness can be predicted and such determinations will only be forthcoming through carefully controlled clinical trials. Such trials may be indicated not only in patients with limited disease, but also in patients with advanced disease who have tumor types other than those which failed to respond in the current study.

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