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NEPHRECTOMY FOLLOWED BY INTERFERON ALFA-2b COMPARED WITH INTERFERON ALFA-2b ALONE FOR METASTATIC RENAL-CELL CANCER

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ABSTRACT

Background The value of nephrectomy in metastatic renal-cell cancer has long been debated. Several nonrandomized studies suggest a higher rate of response to systemic therapy and longer survival in patients who have undergone nephrectomy.

Methods We randomly assigned patients with metastatic renal-cell cancer who were acceptable candidates for nephrectomy to undergo radical nephrectomy followed by therapy with interferon alfa-2b or to receive interferon alfa-2b therapy alone. The primary end point was survival, and the secondary end point was a response of the tumor to treatment.

Results The median survival of 120 eligible patients assigned to surgery followed by interferon was 11.1 months, and among the 121 eligible patients assigned to interferon alone it was 8.1 months (P=0.05). The difference in median survival between the two groups was independent of performance status, metastatic site, and the presence or absence of a measurable metastatic lesion.

Conclusions Nephrectomy followed by interferon therapy results in longer survival among patients with metastatic renal-cell cancer than does interferon therapy alone. (N Engl J Med 2001;345:1655-9.)

IT is unknown whether removal of the primary tumor (cytoreductive surgery) is beneficial in metastatic renal-cell cancer.[1-6] The disease has a poor prognosis and resists conventional chemotherapy, but spontaneous regression occasionally occurs.[7] For these reasons, aggressive surgery has been advocated, especially when solitary or resectable metastatic lesions are present or in patients with a primary tumor in situ whose metastases have responded to interleukin-2.[8,9] Nevertheless, no study has clearly demonstrated that nephrectomy is advantageous in metastatic renal-cell cancer.[5,6]

There are indications that patients with metastatic renal-cell cancer who are treated with interferon alfa or other cytokines have improved outcomes if they first undergo nephrectomy.[10,11] Patients who undergo nephrectomy followed by immunotherapy with interleukin-2, with or without tumor-infiltrating lymphocytes, also survive longer than historical controls.[12-15] However, none of the reports were studies based on prospective, controlled trials.

In 1989, the Southwest Oncology Group (SWOG) initiated a study to determine whether nephrectomy affects survival in metastatic renal-cell cancer. We report the results of this randomized trial.

METHODS

Study Patients

Eligible patients had a histologically confirmed diagnosis of metastatic renal-cell carcinoma in tissue obtained by needle biopsy or needle aspiration of at least one measurable lesion or the primary tumor and had metastases beyond the regional lymphatics; that is, metastatic disease involving a tumor of any size and any nodal status. The primary tumor was considered amenable to surgical extirpation by the attending surgeon. Patients with thrombosis of the inferior vena cava below the hepatic veins were not excluded.

A performance status of 0 or 1 according to the SWOG criteria was required, and patients were excluded if they had received prior treatment with chemotherapy, hormonal therapy, interferon, interleukin-2, lymphocyte-activated killer cells, or other biologic-response modifiers. In addition, prior or concomitant radiation therapy to the primary tumor or to metastatic sites was not allowed. A serum bilirubin level no higher than three times the upper limit of the normal value at the institution and a serum creatinine level of no more

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than 3.0 mg per deciliter (265 μmol per liter) were required. Patients with uncontrolled cardiac arrhythmias were not eligible. Patients who had previously had cancer were also excluded unless they had been free of cancer for at least five years or unless their cancer was adequately treated basal-cell skin cancer, squamous-cell skin cancer, or in situ cervical cancer. All patients provided written informed consent, and the trial was approved by the institutional review board at each institution.

Assessment and Treatment

Before randomization, patients were stratified according to SWOG performance status (0 vs. 1), the presence or absence of lung metastases only, and the presence or absence of at least one measurable metastatic lesion in the region not to be resected. The patients were randomly assigned by a central computer to one of the two groups with dynamic balancing based on the stratification factors.[16]

The patients either underwent immediate radical nephrectomy followed by therapy with interferon alfa-2b (Intron-A, Schering-Plough, Kenilworth, N.J.) (surgery-plus-interferon group) or were given immediate interferon alfa-2b therapy without surgery (interferon-only group).

The dosages of subcutaneous interferon alfa-2b were as follows. Induction therapy was begun at 1.25 million IU per square meter of body-surface area, with escalation to a starting dose of 5 million IU per square meter on the first day of treatment (1.25 million IU per square meter three days before, 2.5 million IU per square meter two days before, and 3.75 million IU per square meter the day before treatment). Interferon was to be continued at a dose of 5 million IU per square meter each Monday, Wednesday, and Friday until progression of the tumor was detected. On each day of treatment, the dosage was modified if any toxic effects were observed, and the modified dosage was continued until resolution of the toxic effects. In the case of two or more toxic effects in the same category, dosage modification was based on the highest-grade toxic effect observed. The toxic effects specifically monitored included hematologic, hepatic, and gastrointestinal effects (e.g., diarrhea and anorexia) and hypotension.

Radical nephrectomy was performed through a transabdominal, flank, or thoracoabdominal approach. It was defined as the excision of the tumor outside Gerota's fascia, with early ligation of the renal artery and vein. The surgery was performed within four weeks of enrollment. The limits of lymphadenectomy were not defined. The surgeon noted whether grossly involved lymph nodes were left unresected at the time of nephrectomy. Responses to treatment (a complete response, a partial response, a stable condition, progression, and an unconfirmed response) were defined according to the criteria of the SWOG.[17]

Statistical Analysis

The trial was planned with survival as the primary end point, a one-sided probability of a type I error of 0.05, and a power of 0.85, and it was based on the assumptions that the median survival would be one year in the interferon-only group and that survival in the surgery-plus-interferon group would be 33 percent lower (hazard ratio for survival, 0.67). A one-sided null hypothesis was used to plan the study, because an additional clinical question was addressed: Is there a benefit to nephrectomy before systemic therapy? We calculated that the trial would require 244 patients enrolled over a period of three years, with one year of follow-up. Two formal interim analyses were planned and were performed without interruption of the trial. This article reports the final analysis of the trial. The criterion we used for significance with respect to the primary end point was $P=0.04$ (one-sided, with adjustment for the interim analyses). Although the design and monitoring of this trial were based on a one-sided null hypothesis, two-sided P values are reported throughout so as to conform to the *Journal*'s policy of reporting only two-sided P values.

The primary analysis concerns survival among eligible patients in the two groups. Eligibility was based only on data collected before randomization. The planned primary analysis was performed with the stratified log-rank test (one-sided), with use of the stratification factors identified above.[18] The analyses in this article are based on data obtained through March 2000.

RESULTS

Between June 1991 and October 1998, 246 patients from 80 participating institutions were randomly assigned to two groups of 123 each. Five patients were found to be ineligible because the pathological diagnosis had been incorrect (three in the surgery-plus-interferon group and two in the interferon-only group). For an additional 16 patients (8 in the surgery-plus-interferon group and 8 in the interferon-only group), the data were insufficient for the determination of eligibility; data from these 16 patients were included in the analysis, but the data on the 5 patients who did not have renal-cell cancer were excluded.

Table 1 shows relevant characteristics of the patients at the time of enrollment. There were no significant imbalances except with respect to performance status ($P=0.04$).

Of the 120 patients in the surgery-plus-interferon group, 17 did not undergo the planned surgery: 7 refused, 5 were found to be medically ineligible for surgery, 3 had unresectable primary tumors, and 2 died before surgery could be performed. Ninety-eight patients were evaluated for complications of nephrectomy. One patient with an unresectable tumor died of wound dehiscence and intraabdominal abscess with peritonitis; two patients had cardiac ischemia or infarction, two had postoperative infections, and one had hypotension. Sixteen patients had only mild-to-moderate complications. No surgical complications were reported in 76 of the 98 patients. The mean duration of hospitalization for nephrectomy was 8.2 days (range, 3 to 22). The mean time to the initiation of interferon alfa-2b therapy in patients who underwent nephrectomy was 19.9 days.

Two eligible patients, one in each group, declined interferon therapy. Two hundred ten patients were evaluated for toxic effects of interferon. One patient in the interferon-only group died of myocardial infarction attributed to interferon. Twenty-three patients (10 in the surgery-plus-interferon group and 13 in the interferon-only group) had severe complications due to interferon.

Among the 92 patients in the surgery-plus-interferon group whose responses could be evaluated and who had a measurable lesion at base line, three partial responses were reported (3.3 percent; 95 percent confidence interval, 1 to 9 percent), and among the 83 comparable patients in the interferon-only group, three responses were reported (one complete, one partial, and one unconfirmed; 3.6 percent; 95 percent confidence interval, 1 to 10 percent). Of the 175 patients with a measurable lesion at base line, 65 (37 percent) had inadequate data for assessment of the response,

TABLE 1. CHARACTERISTICS OF THE 241 ELIGIBLE PATIENTS.

CHARACTERISTIC	INTERFERON ALONE (N=121)	NEPHRECTOMY PLUS INTERFERON (N=120)
Age (yr)		
Mean	59.0	58.8
Range	29–87	37–80
Male sex (%)	69.4	69.2
Measurable metastatic lesion (%)	75.2	81.7
Performance status 1 (%)*	58.1	45.0†
Only lung metastases (%)	66.9	65.8

*Performance was scored as 0 or 1, with 1 indicating decreased activity.

†P=0.04 for the comparison with the interferon-only group.

and they were assumed not to have had a response. There were no differences between the two groups with respect to the proportion with a response to interferon alfa-2b. The response rates in both groups in this study were lower than those generally reported.[19,20] The most likely explanation for this difference is that the SWOG criteria for a response are more rigorous than the criteria generally used.[17]

At the time of our analysis of the study data, only 20 of the 241 eligible patients were alive, with a median follow-up of 368 days. Table 2 shows the estimated median survival times, the Kaplan–Meier estimates of survival at one year, and the one-sided P values (derived by the log-rank test) according to group and stratification factors. Figure 1 shows actuarial survival in the two groups.

The primary analysis, based on the stratified log-rank test, found a significant advantage associated with nephrectomy (P=0.05) (Table 2), with two-sided P values. The median overall survival was 8.1 months in the interferon-only group (95 percent confidence interval, 5.4 to 9.5) and 11.1 months in the surgery-plus-interferon group (95 percent confidence interval, 9.2 to 16.5).

The survival advantage associated with nephrectomy was evident in subgroups defined according to all three stratification factors (Table 2). The imbalance with respect to performance status at randomization (Table 1) could explain the overall difference in survival, since patients with a performance status of 1 (those with a worse prognosis) were overrepresented in the interferon-only group. However, the differences in median survival favor the surgery-plus-interferon group among patients with each performance status: 17.4 and 11.7 months for performance status 0 in the surgery-plus-interferon and interferon-only groups, respectively, and 6.9 and 4.8 months for performance status 1. In a proportional-hazards regression model that included treatment group, performance status, and the interaction between treatment group and performance status, the interaction term was not significant — an indication that the imbalance did not explain the primary result.

DISCUSSION

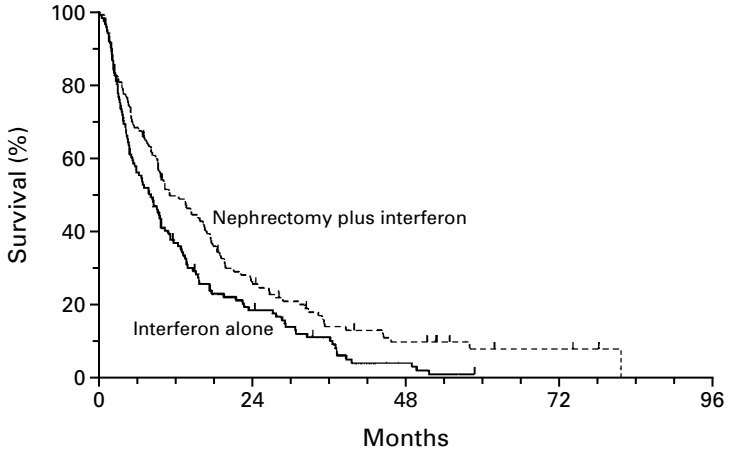
This study provides evidence that nephrectomy before interferon alfa-2b therapy for metastatic renal-cell cancer confers a survival benefit. Metastatic renal-cell cancer is very difficult to treat effectively, because of its unpredictable behavior and resistance to chemotherapy. Yagoda et al. reviewed a large series of trials of chemotherapeutic regimens and found a 5.6 percent

TABLE 2. SURVIVAL IN SUBGROUPS DEFINED ACCORDING TO STRATIFICATION FACTORS.

CATEGORY	MEDIAN SURVIVAL		1-YR SURVIVAL		P VALUE*
	INTERFERON ALONE	NEPHRECTOMY PLUS INTERFERON	INTERFERON ALONE	NEPHRECTOMY PLUS INTERFERON	
	mo		%		
Not stratified	8.1	11.1	36.8	49.7	0.012
Stratification factor					
Measurable disease					0.010
Yes	7.8	10.3	34.7	46.6	
No	11.2	16.4	43.1	63.6	
Performance status†					0.080
0	11.7	17.4	49.2	63.6	
1	4.8	6.9	28.2	32.5	
Type of metastases					0.008
Lung only	10.3	14.3	41.5	58.5	
Other	6.3	10.2	34.6	45.1	

*P values for the comparison of median survival between groups were derived with the log-rank test.

†Performance was scored as 0 or 1, with 1 indicating decreased activity.



No. at Risk					
Interferon alone	121	21	4	0	
Nephrectomy plus interferon	120	29	9	3	0

Figure 1. Actuarial Survival among All Eligible Patients, According to Treatment-Group Assignment.
In the interferon-only group, there were 115 deaths and median survival was 8.1 months. In the surgery-plus-interferon group, there were 106 deaths and median survival was 11.1 months.

rate of objective response to cytotoxic agents in 3502 adequately treated patients.[21] There are, however, indications of improved survival with chemotherapy after nephrectomy.[22] Moreover, previous trials of biologic-response modifiers in metastatic renal-cell cancer have consistently shown an improved response rate or improved survival after removal of the primary tumor.[2,12,23,24] The interval from nephrectomy to the systemic treatment of the renal-cell cancer was not controlled in these series, thus raising the question whether nephrectomy had a biologic effect or whether patients selected for nephrectomy had tumors that would probably respond to systemic treatment. The effect of nephrectomy may, however, be real. Several reports of immunotherapy for renal-cell cancer, with or without concomitant chemotherapy, have supported the idea that patients who undergo nephrectomy before systemic treatment have a survival advantage.[14,25,26]

Recently, the combination of nephrectomy, tumor-infiltrating lymphocytes, and cytokine therapy in metastatic renal-cell cancer has yielded a response rate of 33.9 percent (12.5 percent complete responses and 21.4 percent partial responses)[11] and two-year and three-year survival rates of 40 percent and 31 percent, respectively, among patients treated in this aggressive manner.[15] Why nephrectomy before systemic therapy might be effective is unknown. A recent study by Fujikawa et al. suggests that only patients with elevated serum C-reactive protein levels may benefit from cytoreduction by nephrectomy.[13]

One argument against the use of nephrectomy before therapy with a biologic-response modifier has been the high operative morbidity and mortality rate. Although earlier series reported mortality rates of 6 to 11 percent,[27,28] there was only one operative death in our study (less than 1.0 percent), and the rate of severe complications with surgery in our trial (4.9 percent; five patients) compares favorably with rates in other studies.[11] Furthermore, there is no evidence that nephrectomy delayed systemic treatment in a way that would offset the survival benefit associated with the surgery (mean hospitalization time, 8.2 days; mean time to initiation of interferon alfa-2b therapy, 19.9 days).

We believe that nephrectomy in suitable patients should be an eligibility criterion in trials of new systemic agents for the treatment of metastatic renal-cell cancer. We also believe that nephrectomy followed by therapy with interferon alfa-2b (with or without other cytokines) should be considered the standard of care (i.e., should be used in the control group) in future phase 3 trials.

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