Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial

G H J Mickisch, A Garin, H van Poppel, L de Prijck, R Sylvester, and members of the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group

Summary

Background Surgery is the main treatment for localised renal cell carcinoma, but use of radical nephrectomy for metastatic disease is highly controversial. We aimed to establish whether radical nephrectomy done before interferon-alfa-based immunotherapy improved time to progression and overall survival (primary endpoints) compared with interferon alfa alone.

Methods We included 85 patients from June, 1995, to July, 1998: two (one per group) were ineligible. 42 of the 83 participants were randomly assigned combined treatment (study group) and 43 immunotherapy alone (controls). All patients had metastatic renal-cell carcinoma that had been histologically confirmed and was progressive at entry. In study patients, surgery was done within 4 weeks of randomisation, and immunotherapy (5×10^6 IU/m^2 subcutaneously three times per week) started 2–4 weeks later. In controls, immunotherapy was started within 1 working day of randomisation. Follow-up visits were monthly. All analyses were by intention to treat.

Findings 40 (53%) of 75 patients received at least 16 weeks of interferon-alfa treatment, which was also the median duration of treatment. Time to progression (5 vs 3 months, hazard ratio 0·60, 95% CI 0·36–0·97) and median duration of survival were significantly better in study patients than in controls (17 *vs* 7 months, 0·54, 0·31–0·94). Five patients responded completely to combined treatment, and one to interferon alfa alone. Dose modification was necessary in 32% of patients, most commonly because of non-haematological side-effects.

Interpretation Radical nephrectomy before interferon-based immunotherapy might substantially delay time to progression and improve survival of patients with metastatic renal cell carcinoma who present with good performance status.

Lancet 2001; **358:** 966–70
See Commentary page 948

Erasmus University and Academic Hospital Rotterdam-Dijkzigt, Rotterdam, Netherlands (Prof G H J Mickisch MD)**; Cancer Research Center, Moscow, Russia** (Prof A Garin MD)**; U Z Gasthuisberg, Leuven, Belgium** (Prof H van Poppel MD)**; and EORTC Data Centre, Brussels, Belgium** (L de Prijck, R Sylvester DSc)

Correspondence to: Prof G H J Mickisch, Department of Urology, Erasmus University and Academic Hospital Rotterdam-Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, Netherlands (e-mail: mickisch@urol.azr.nl)

Introduction

At diagnosis, about 20% of patients with renal-cell carcinoma have disseminated disease, and another 25% have locally advanced disease. About a third of patients with tumour of the kidney at diagnosis will develop metastatic disease postoperatively. Thus, some 50% of all patients with renal-cell carcinoma will eventually present with disease that requires complex treatment decisions.[1] Radical nephrectomy is the preferred treatment in organ-confined stages of disease.[2] However, because curative surgery is almost impossible in disseminated disease, the benefits of surgery to a patient with metastatic renal-cell carcinoma have been disputed. With arrival of modern immunotherapies, albeit of restricted efficacy, we need to critically reassess surgical treatment of metastatic renal-cell carcinoma.[3,4]

The effect of nephrectomy before immunotherapy in patients with renal-cell carcinoma has not been measured. The theoretical advantages include reduction in the number of cancerous cells, removal of a trap for trafficking lymphocytes, prevention of complications during systemic treatment, opportunity to harvest tumour-infiltrating lymphocytes and tumour cells for use in experimental treatments, and reduction of a large and potentially immunosuppressive tumour burden. Other potential advantages include improvement in performance status score of patients, better tolerance and higher probability of response to immunotherapy, elimination of the primary tumour as a possible source of haemorrhage, discomfort, or propagation of metastases, and the fact that responses to immunotherapy in the primary disease site have been rare. Potential disadvantages include growth of metastatic disease in the recovery period that could preclude treatment, and morbidity associated with any major operation.[5,6]

We aimed to address the issues of whether combined treatment lengthens time to progression and confers a survival benefit, and, secondarily, whether nephrectomy before immunotherapy increases the response rate to immunotherapy. Two randomised trials were done with the same eligibility criteria, treatments, and design: European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group trial 30 947, and Southwest Oncology Group (SWOG) trial 8949. We report results for the patients in the EORTC study. Results for participants in the SWOG trial have been reported elsewhere.[7]

Methods

Participants

All patients had a diagnosis of metastatic renal-cell carcinoma that had been histologically confirmed (needle biopsy or needle aspiration biopsy of at least one metastatic lesion or of the primary tumour). Inclusion criteria were metastases that extended beyond regional lymphatics (ie, any tumour, node, or metastatic 1 disease), measurable or evaluable disease in a region that could not be resected with standard nephrectomy procedures, and a primary renal-cell

carcinoma that could have been surgically removed if the patient had not had metastatic disease. We did not exclude patients with infradiaphragmatical caval thrombus who were candidates for surgery, or those with tumour thrombus in the renal vein. Patients with evidence of brain metastasis were ineligible. Patients with bone metastases had a bone scan within 14 days before registration.

Other eligibility criteria included a performance status of WHO 0 or 1; no previous or concomitant treatment with chemotherapy, hormonal therapy, interferon, interleukin 2, lymphokine-activated-killer-cell therapy, or other biological-response modifiers; adequate liver function (serum bilirubin concentration ≤three times the relevant institution's upper normal limit); adequate renal function (serum creatinine ≤265 μmol/L); and a white-blood-cell count of at least 4×10^6/L and a platelet count of at least the institution's lower normal limit. Previous treatment with thyroid drugs was allowed. No previous or concomitant radiation therapy was allowed for the primary tumour or for metastatic disease (apart from palliative radiation for areas of painful metastases that was outside all areas of measurable or evaluable disease being used for response assessment). Exclusion criteria included previous malignant disease apart from adequately treated basal-cell or squamous-cell skin cancer, in-situ cervical cancer, or other cancer for which the patient had been disease free for at least 5 years; uncontrolled cardiac arrhythmias; pregnancy or lactation; and refusal to use an effective method of contraception.

All institutions were members of the EORTC GU Group and had undergone quality-control assessment by the EORTC. Every local institution review committee approved the protocol, and every centre was responsible for drug accountability and reporting of adverse events. All patients gave written informed consent before study enrolment.

Procedures

Patients were randomly assigned to nephrectomy and immunotherapy (study group) or immunotherapy alone (controls) with a dynamic minimisation allocation scheme.[8] Treatment assignment was stratified by institution, performance status; WHO status 0 (fully active) or status 1 (restricted in physically strenuous activity but able to do light or sedentary work), presence of lung metastases only, and measurable or evaluable disease in a region that could not be resected with standard nephrectomy procedures.

Study patients who underwent radical nephrectomy had surgery transabdominally via the flank, or thoraco-abdominally. We defined a radical nephrectomy as excision of the tumour outside of Gerota's fascia, with early ligation of the renal artery and vein. Surgery was planned to begin within 4 weeks of randomisation. Limits of the lymphadenectomy were not further defined. The surgeon noted whether grossly affected lymph nodes were left unresected or were completely removed. Any surgical complication was treated routinely. Patients who could not have surgical resection received interferon-alfa-2b treatment and were included in our final intent-to-treat analysis. Study patients randomised to nephrectomy plus interferon alfa-2b started treatment up to 1 month after nephrectomy, with a subcutaneous dose of 5×10^6 IU/m^2 three times per week. Projected treatment duration was 52 weeks or until disease progressed or unacceptable side-effects occurred. Controls received the same immunotherapy as study patients, within 1 working day of randomisation.

Measurable disease, evaluable disease, or both were assessed in all participants at weeks 8, 12, 16, 20, 24, 36, and 52. Palliative radiotherapy in regions not to be used for measurement or evaluation was given if indicated. Patients received treatment until disease progressed, unacceptable side-effects occurred, or patients refused to continue. All patients were followed up until death. Treatment doses were modified if side-effects were seen on day of treatment. Dose modification consisted of reduction by $1{\cdot}25\times10^6$ IU/m^2 for a maximum of three reductions. Treatment was resumed on the next scheduled day for treatment at the reduced level. In the case of two or more side-effects in the same category, dose modification was based on the worst effect. Patients with grade 3 or 4 non-haematological side-effects did not receive further interferon until resolution of the adverse reaction. Treatment was stopped if the same side-effect reoccurred despite dose reduction.

Patients had to have recovered from any surgical complications before interferon-alfa-2b therapy was started. Specified complications included longlasting ileus, wound infection, blood loss, small bowel obstruction, flank pain, incisional hernia, and pneumothorax.

Measurable disease was defined as lesions that could be measured in two dimensions with margins clearly defined in medical photographs (skin lesion), in radiographs, or in scans with at least one diameter greater than 0·5 cm (not bone lesions); or palpable lesions with both diameters 2 cm or greater. We defined evaluable disease as lesions that could be measured in one dimension, masses with margins not clearly defined, palpable lesions with either diameter less than 2 cm, any lesion with both diameters less than 0·5 cm, or bone disease. Non-evaluable disease included pleural effusions, ascites, and disease documented by indirect evidence only (eg, by laboratory values).

A complete response was the complete disappearance of all measurable and evaluable disease; no new lesions; no disease-related symptoms; and no evidence of non-evaluable disease, including normal concentrations of markers and other abnormal laboratory test results. All measurable, evaluable, and non-evaluable lesions and sites were assessed. A partial response applied only to patients with at least one measurable lesion and was defined as at least a 50% decrease from baseline in the sum of the products of perpendicular diameters of all measurable lesions, no progression of evaluable disease, and no new lesions. All measurable and evaluable lesions and sites were assessed. Patients defined as having a stable response or no response had no complete or partial response, or progression. All measurable and evaluable sites and lesions were assessed.

We defined progression as a 50% or 10 cm^2, whichever was smaller, increase in the sum of products of measurable lesions from the smallest sum noted (from baseline if no decrease took place); reappearance of any lesion which had disappeared; clear worsening of any evaluable disease; appearance of any new lesions or sites; and failure to return for assessment because of deteriorating condition—unless deterioration was clearly unrelated to the cancer. We calculated best response from the sequence of objective response statuses that we recorded. Two assessments of complete response, partial response, stable disease, or progressive disease were defined as a best response of this disease status. All patients were graded according to the WHO performance status scale.

Statistical analysis

With the assumption of median survival of 1 year for interferon alfa-2b alone, a one-sided α at a 0·05 level of significance (log-rank test) with power of 0·85 for detection of a 50% improvement with nephrectomy (or power of 0·80 for detection of a 45% improvement with nephrectomy), with 3 years of recruitment of patients and another year of follow-up, required 244 patients (planned in the original

	Study group (n=42)	Control group (n=42)	Both groups (n=84)
Characteristic			
Age (median [range], years)	61 (36–76)	56 (29–74)	59 (29–76)
Men	33 (79%)	27 (64%)	60 (71%)
Women	9 (21%)	15 (36%)	24 (29%)
WHO performance score			
0	20 (48%)	17 (40%)	37 (44%)
1	22 (52%)	25 (60%)	47 (56%)
Primary tumour characteristics			
Extension			
Perirenal tissue	13 (31%)	16 (38%	29 (35%)
Adrenal gland	5 (12%)	5 (12%)	10 (12%)
Venous invasion	8 (19%)	11 (26%)	19 (23%)
Inferior vena cava	2 (5%)	4 (10%)	6 (7%)
Beyond Gerota's fascia	7 (17%)	9 (21%)	16 (19%)
Tumour size			
<5 cm	4 (10%)	5 (13%)	9 (11%)
5–9 cm	16 (39%)	20 (50%)	36 (44%)
10–14 cm	17 (41%)	14 (35%)	31 (38%)
>15 cm	4 (10%)	1 (3%)	5 (6%)
Metastatic sites			
Distant nodes	11 (26%)	18 (43%)	29 (35%)
Lung or pleura	33 (79%)	34 (81%)	67 (80%)
Liver	5 (12%)	4 (10%)	9 (11%)
Other abdominal	4 (10%)	5 (12%)	9 (11%)
Skin or subcutaneous	2 (5%)	2 (5%)	4 (5%)
Bone	9 (21%)	10 (24%)	19 (23%)
Central nervous system	0	1 (2%)	1 (1%)

Number of patients (%) shown, unless otherwise stated.

Table 1: **Baseline characteristics**

SWOG protocol). The EORTC planned to recruit 80 patients for this study.

With 122 patients per group, there was an 85% power to detect an improvement in response rate from 15% to 30%. Primary lesions could not be used as index lesions. All randomised patients were included in the analysis (intent to treat). The study was designed by the SWOG with one-sided tests, but the EORTC decided to compare response rates based on a two-sided Fisher's exact test for differences in proportions. Time to progression and duration of survival curves were estimated with the Kaplan-Meier method and compared by two-sided log-rank tests.

Results

From June, 1995, to July, 1998, the EORTC randomised 85 patients. Two were ineligible, one from each treatment group. Of the remaining 83 patients, 42 were randomised to surgery plus immunotherapy (study group) and 43 to receive immunotherapy alone (controls). Figure 1 shows the trial profile. No data were available for one control patient. Both groups were similar with respect to age, sex, WHO-performance score (0 or 1), tumour type, venous invasion, lung metastases only (stratification factor), liver metastases, bone metastases and comorbidity (table 1). 20 patients were younger than 50 years, 12 older than 70 years. Four study patients had no tumour nephrectomy and received immunotherapy whenever possible.

	Study group (n=34)	Control group (n=41)	Both groups (n=75)
Duration (median [range], weeks)	16 (1–90)	12 (4–54)	16 (1–90)
Dose modification*	15 (44%)	9 (22%)	24 (32%)
Haematological	4 (12%)	2 (5%)	6 (8%)
Non-haematological	10 (29%)	6 (15%)	16 (21%)
Not drug related	7 (21%)	5 (12%)	12 (16%)

*Data are number of patients (%).

Table 2: **Interferon treatment**

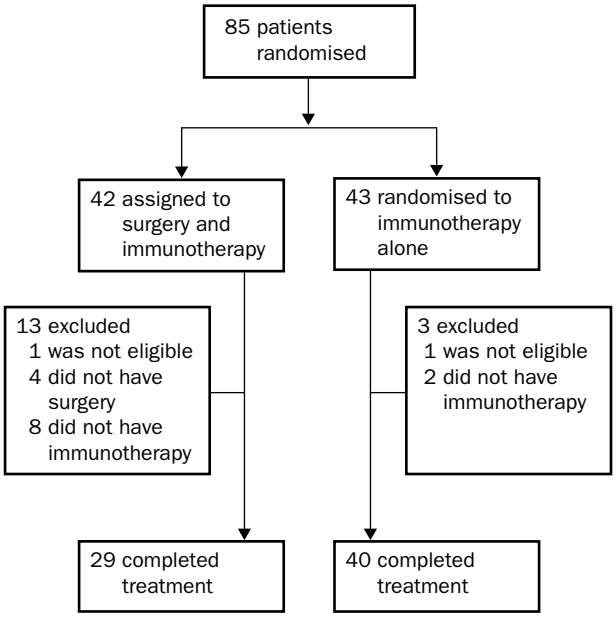


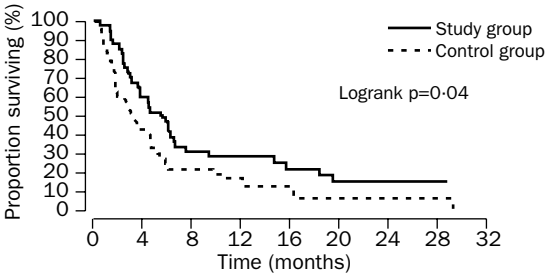
Figure 1: **A trial profile**

Six patients (designated here as A–F) had perioperative surgical complications, and one of them did not receive adequate immunotherapy. Patient A had a wound infection requiring local conservative treatment. Immunotherapy was started within 1 month after surgery in accordance with protocol requirements, and was continued for 61 weeks without any dose reductions. Patient B had a postoperative pneumothorax with atelectasis of the left lung requiring insertion of a thoracic drain until complete recovery. Immunotherapy was started 5 weeks after nephrectomy (minor protocol violation), and was continued for a total of 100 weeks. At week 20, a dose reduction of one dose level was necessary because of haematological side-effects of interferon therapy. Patient C had lung atelectasis and a bronchopneumonia requiring conservative treatment until resolution. Immunotherapy was started within 1 month after surgery, and was continued for a total of 24 weeks without dose reductions. Patient D had fever (grade II) of unknown origin which resolved spontaneously. Immunotherapy was started within 1 month after surgery, and was continued for a total of 52 weeks. At week 36, a dose reduction of one dose level was necessary because of haematological side-effects of interferon therapy. Patient E had cardiac problems requiring cardioversion 4 days after surgery. Immunotherapy was started within 1 month after nephrectomy, and was continued for a total of 105 months without dose reductions. Patient F developed a cerebellar syndrome with distinct ataxia postoperatively. Additionally, progressive disease from bone metastasis was detected 1 week after operation and patient F did not receive immunotherapy. This patient died 6 weeks after nephrectomy.

	Study group (n=42)	Control group (n=43)
Complete	5	1
Partial	3	4
No change	17	18
Progression	14	14
Unknown	3	6

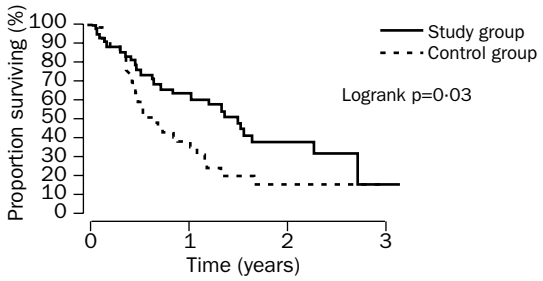
Comparison of response rates: 19% *vs* 12%, p=0·38.

Table 3: **Response rates**



	Observed number of events	Number of patients at risk						
Study group	32	42	23	12	10	7	4	2	1
Controls	37	42	17	8	5	2	1	1	1

Figure 2: **Kaplan-Meier curves showing time to progression**
O=Observed number of events.



	Observed number of events	Number of patients at risk			
Study group	25	42	22	7	1
Controls	30	42	12	2	0

Figure 3: **Kaplan-Meier curves showing overall survival**
O=Observed number of events.

In general, large tumours (median diameter 11·5 cm) were operated on, resulting in a large reduction of tumour burden before immunotherapy. Side-effects such as myelotoxicity, nausea, anorexia, and neurological or psychological disorders were equally distributed between treatment groups, and led to a dose modification in 32% (24 of 75) of patients, but were generally thought manageable in an outpatient setting. 53% (40 of 75) of all patients received at least 16 weeks of interferon-alfa treatment (table 2).

Five study patients and one control had complete responses (table 3). Partial responses and stable disease were similarly distributed between treatment groups. Overall objective response rate (complete plus partial response) did not differ between study and control groups, 19% (eight of 42) versus 12% (five of 43), p=0·38. However, study patients had longer time to progression (p=0·04, figure 2) and longer duration of survival than controls (p=0·03, figure 3). Hazard ratio for survival was 0·54 (95% CI 0·31–0·94), and for time to progression was 0·60 (0·36–0·97). The estimate for the median survival improved from 7 months in the control group to 17 months in the study group.

Discussion

Our results clearly show an important survival benefit for nephrectomised patients presenting with a good performance score, whose primary tumour has been assessed to be surgically operable, and who are good candidates for subsequent immunotherapy. Response rates did not differ between nephrectomised patients and those with the primary tumour in situ.

A nephrectomy in a patient with metastatic spread of a renal-cell carcinoma almost certainly will not cure the disease, and the patient will die of these metastases rather than from the primary tumour. In fact, the only rationale in favour of nephrectomy in the presence of metastases is a potential survival benefit, or improvement of quality of survival. But, nephrectomy done in the disseminated disease stage is an operation with known morbidity and sometimes mortality. Increase of lifespan can only be achieved if improved tumour control is obtained by surgery. Nephrectomy will reduce the tumour burden and remove the source of new metastases.

Additionally, nephrectomy has been thought to induce spontaneous regression of metastases. Reports on this effect have been reviewed[9] and overall frequency established as about 0·7%, whereas the mortality of the surgery is 1–5%. Furthermore, spontaneous regression of metastatic lesions can also occur without surgery. We did not note any spontaneous regressions. Moreover, previous nephrectomy can potentially enhance response to systemic therapy, an issue that has remained quite controversial. In a study of 55 patients with metastatic renal-cell carcinoma, triple-drug immunotherapy resulted in a 32% objective response-rate in those who had had nephrectomy, whereas the same regimen had a response rate of only 4·7% with the primary tumour in situ.[10] However, these results do not necessarily show a biological effect of nephrectomy, because patients in this study who were not offered nephrectomy almost certainly had a poor performance score, and thus represented a negative selection bias. Only prospectively randomised trials such as ours can adequately settle the question, "Does surgery improve the response to immunotherapy?". The power of our (EORTC) part of the study by itself is low. Thus, our non-significant difference between response rates should not be interpreted as meaning that there is no difference between treatments, merely that the results are inconclusive. The EORTC results should not be interpreted in isolation from those of SWOG. We are hoping to be able to put together the results of the two parts in a combined analysis.

The second aim of a nephrectomy in metastatic renal-cell carcinoma is to improve quality of life by obtaining relief of symptoms, mainly haematuria, pain, or systemic manifestations. Haematuria can be quite serious, necessitate transfusion, and lead to death. However, not only nephrectomy, but also embolisation could effectively treat this symptom. Pain caused by the primary tumour can result from tumour necrosis; the tumour will eventually haemorrhage and cause evacuation of blood clots with renal colic. In these cases, an improvement in symptoms can be expected from nephrectomy. Mostly, however, pain is due to direct involvement of nerves or bony structures, where surgery will be difficult and not very rewarding.

The systemic manifestations of metastatic renal-cell carcinoma are general deterioration of performance status score, anaemia, anorexia, weight loss, fever, hypertension, and hypercalcaemia. These symptoms, partly paraneoplastic, are very likely to show amelioration after nephrectomy when no metastases are present. In patients with disseminated disease, the effect on these systemic sequelae of renal-cell carcinoma will often not be altered by nephrectomy unless metastases are treated at the same time. Nevertheless, many patients with metastatic disease will have a short general improvement after nephrectomy that temporarily slows progressive deterioration. Further, the intention to prevent symptoms caused by spontaneous rupture and bleeding, or pain is not a valid reason for nephrectomy in metastatic renal-cell carcinoma, since these symptoms can be treated adequately when they arise.

Finally, the choice to leave the primary tumour in place or do major surgery that is potentially useless can depend on psychological factors. The decision to choose surgery or surveillance often depends on a urologist's ability to be honest with advanced cancer patients and to be able to inform them of the stage of their disease. Our trial results might aid the development of a more rational discussion of these complex issues.

In assessment of the controversial issue of cytoreductive surgery before immunotherapy, the questions that must be asked are (1) do patients with metastatic disease tolerate the operation well enough to receive systemic treatment postoperatively? And (2) does removal of the primary tumour increase the likelihood of an objective response to immunotherapy at metastatic sites?[11] Comparison of non-randomised trials shows that the operation, if done by skilledsurgeons, has acceptable mortality and little morbidity.[12,13,14] However, these reports also indicate that from 38% to 77% of patients did not receive immunotherapy, usually because of rapid disease progression. In our trial, only one patient scheduled to receive interferon alfa did not receive the drug.

In an effort to limit size reduction nephrectomy to patients who were most likely to benefit from combined treatment, strict enrolment criteria were established. Patients with inadequate cardiac or pulmonary function, central nervous system metastases, or concurrent illness were excluded because they were ineligible a priori for immunotherapy. Patients were also ineligible if their chance of response would not be significantly improved by removal of the primary tumour because of disease distribution (bone, liver, or contralateral kidney), extent of metastases, or non-clear cell-tumour histology; and if their risk of rapid worsening of symptoms after surgery was increased. In previous studies, these criteria have enabled 87·3%[5] and 93%[15] of selected patients to recover from nephrectomy and to receive immunotherapy. This subset represented 33% or 55%, respectively, of patients presenting with metastatic renal-cell carcinoma. Objective response rates in all studies ranged from 12·6% to 39% with almost all responses[5,12–15] being incomplete. Because these data were from non-randomised studies, any lengthening of survival was inconclusive.[16]

There were few patients in our study, and combination with data from the SWOG[7] would improve precision of the results. Nevertheless, our results are in accord with the results in the SWOG study.[7] The timing and effect of nephrectomy merits further investigation, as does the search for active treatment regimens. However, surgery is always required to ensure that all disease has been eradicated. On the basis of the results of our study and the preliminary report on SWOG 8949, we recommend tumour nephrectomy before immunotherapy as a standard treatment for metastatic renal-cell carcinoma patients, who are suitable for this approach.

Contributors

G H J Mickisch coordinated the trial, was the biggest contributor of patients, and wrote the manuscript. A Garin and H van Poppel contributed patients. L de Prijck managed the data. R Sylvester did statistical anaysis, and advised on scientific matters and the manuscript.

Acknowledgments

This project was supported by grant numbers 5U10 CA11488-24, 2U10 CA11488-25, 5U10 CA11488-26, 5U10 CA11488-27, 2U10 CA11488-28, 5U10 CA11488-29, and 5U10 CA11488-30 from the National Cancer Institute (Bethesda, MD, USA).

References

1 Scheltema JMW, Mickisch GH. Management of metastatic renal cell carcinoma: role of nephrectomy, immunotherapy, failure of chemotherapy and drug resistance. *Europ Urol Update Series* 1997; **6:** 27–33.

2 Mickisch GH. No touch nephrectomy: still a necessity? *Europ Urol Update Series* 1998; **7:** 115–17.

3 Mickisch GH. Immunotherapy of renal cell carcinoma: a critical appraisal from a urologist's point of view. *Urol Int* 1999; **63:** 16–21.

4 O'Connell JR, McCaffrey JA, Motzer RJ. What is the role of nephrectomy in patients with metastatic renal cell carcinoma? *Semin Oncol* 1996; **23:** 17–28.

5 Bennett RT, Lerner SE, Taub HC. Cytoreductive surgery for stage IV renal cell carcinoma. *J Urol* 1995; **154:** 32–34.

6 Fallick ML, McDermott DF, LaRock D. Nephrectomy before interleukin-2 therapy for patients with metastatic renal cell carcinoma. *J Urol* 1997; **158:** 1691–95.

7 Flanigan RC, Blumenstein BA, Salmon S, et al. Cytoreductive tumornephrectomy in metastatic renal cancer: the results of Southwest Oncology Group Trial 8949. *J Urol* 2000; **163** (suppl)**:** 685 (abstr).

8 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in controlled clinical trial. *Biometrics* 1975; **31:** 103–15.

9 Van Poppel H, Baert L. Nephrectomy for metastatic renal cell carcinoma and surgery for distant metastases. *Acta Urol Belgica* 1996; **64:** 11–17.

10 Joffe JK, Banks RE, Forbes MA. A phase II study of interferon α, interleukin-12 and 5-fluorouracil in advanced renal cell carcinoma: clinical data and laboratory evidence of protease activation. *Br J Urol* 1996; **77:** 638–49.

11 Wagner JR, Walther MM, Linehan WM, White DE, Rosenberg SA. Interleukin-2 based immunotherapy for metastatic renal cell carcinoma with the kidney in place. *J Urol* 1999; **162:** 43–45.

12 Walther MM, Yang JC, Pass HI. Cytoreductive surgery before high dose interleukin-2 based therapy in patients with metastatic renal cell carcinoma. *J Urol* 1997; **158:** 1675–78.

13 Tigrani VS, Reese DM, Small EJ, Presti JC Jr, Carroll PR. Potential role of nephrectomy in the treatment of metastatic renal cell carcinoma: a retrospective analysis. *Urology* 2000; **55:** 36-40.

14 Walther MM, Lyne JC, Libutti SK, Linehan WM. Laparoscopic cytoreductive nephrectomy as preparation for administration of systemic interleukin-2 in the treatment of metastatic renal cell carcinoma: a pilot study. *Urology* 1999; **53:** 496–501.

15 Taneja SS, Pierce W, Figlin R. Immunotherapy for renal cell carcinoma: the era of interleukin-2 based treatment. *Urology* 1995; **45:** 911–14.

16 Motzer RJ, Mazumdar M, Bacik J, Russo P, Berg WJ, Metz EM. Effect of cytokine therapy on survival for patients with advanced renal cell carcinoma. *J Clin Oncol* 2000; **18:** 1928–35.