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# Metastatic Renal Cell Carcinoma (RCC): Spontaneous Regression, Long-term Survival and Late Recurrence

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We report 4 cases of metastatic renal cell carcinoma (RCC) with long-term survival either following radical nephrectomy alone or in combination with radio- or hormonal therapy.

Two patients with lymph node metastases showed a long-term survival of 12 or more years following radical tumour nephrectomy (with lymphadenectomy) and radiotherapy. One of them exhibited a histologically proven tumour recurrence nearly 12 years after primary surgical treatment and died shortly later; the other one is still without any evidence of metastatic disease.

Two other patients exhibited spontaneous regression of pulmonary metastases: one regression occurred after radical tumour nephrectomy alone, the other one after successful primary hormonal treatment and subsequent radical tumour nephrectomy.

The following important aspects are emphasized:

1. Renal cell carcinoma is a very unpredictable tumour. Once the diagnosis of renal cell carcinoma is proved, a patient can never be considered cured.

2. Although adjuvant palliative nephrectomy has produced contradictory results in several reports, radical tumour nephrectomy either alone or in combination with other adjuvant therapies such as radiotherapy, hormonal or immunological treatment, can be worthwhile. Cases with long-term survival and spontaneous regression of distant metastases are proof of this. Besides, if carefully selected, the mortality rate of different adjuvant therapies is not significantly higher in patients with metastatic disease than in patients without metastases.

The world literature on this subject is reviewed.

## Introduction

Renal cell carcinoma (RCC) is an aggressive, and unpredictable tumour. Symptoms quite often do not occur until the tumour has already progressed quite far. At diagnosis about one third of all patients have already got distant metastases [16, 24], most commonly involving the lungs, liver, long bones and brain [16]. How to treat these patients has been the question for a number of decades. In the last 20 years treatment has consisted of radical nephrectomy either alone or combined with some sort of adjuvant therapy such as radio-, hormonal, chemo- or most recently immunotherapy. All these therapies have

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been tried with big hopes at first, but later have not lived up to expectations. So what is left is radical nephrectomy, sometimes in combination with one of the mentioned therapies, e.g. radiotherapy (Cases 1 and 2) or hormonal treatment (Case 4).

Adjuvant palliative nephrectomy has produced contradictory results in several reports [15, 20, 21]. Their authors are not in favour of adjuvant nephrectomy as they have not observed spontaneous regression or long-term survival among their cases. Only Mims et al. [21] described one case of spontaneous regression of bone metastases in a group of 97 patients. At our Department, however, 4 cases (3.6%) out of 110 with metastatic renal cell carcinoma (RCC) have shown this phenomenon following either radical tumour nephrectomy alone or in combination with an adjuvant therapy. Therefore our data correspond with the world literature in which the spontaneous regression rate of metastatic RCC ranges from 0.4 to 4%. Two of our 4 cases have exhibited a long-term survival of 12 years or more in spite of histologically proven lymph node metastases (probably due to spontaneous regression), the other 2 have shown spontaneous regression of pulmonary metastases [8]. So far most cases of spontaneous regression of metastatic RCC have been spontaneous regressions of pulmonary metastases following radical tumour nephrectomy.

The following 4 cases are supporting the thesis that radical tumour nephrectomy – sometimes in combination with other adjuvant therapies – is worthwhile trying, whereas a therapeutical nihilism is not justified.

## Case reports

*Case 1.* In October 1976, a 63-year-old woman had an accident in which she suffered fractures of the thoracic vertebrae VIII and XII. In hospital routine laboratory investigations revealed polyglobulia with haemoglobin between 21 and 22 g%. Subsequent bone marrow tap suggested polycythaemia vera. She was therefore transferred to the Medical Department for further investigation. A few days later she developed macrohaematuria that persisted for several days. IVU and abdominal ultrasound led to the suspicion of a solid mass in the lower pole of the left kidney. The patient was transferred to our Urological Department; here a CAT scan, cystoscopy and angiography confirmed the diagnosis of renal cell carcinoma (RCC) of the left lower pole. After a course of preoperative radiotherapy, left radical transperitoneal tumour nephrectomy was performed in December 1976.

The removed kidney weighed 590 g and contained a large mass of $10 \times 6 \times 5$ cm in the lower pole with strong regressive alterations, scars and calcifications. Histology revealed clear cell renal cell carcinoma with ample necrosis and huge local lymph node metastasis. Postoperatively the patient made an uneventful recovery.

At follow-up there was no evidence of relapsing tumour until May 1988.

At that time she developed a slowly progressive leg-accentuated flabby left hemiparesis in the course of several weeks; she also became temporarily confused. A CAT scan of her brain, taken as an out-patient several weeks prior to hospital admission revealed two hypodense lesions in the right parietal and frontal lobe that were enriched with contrast medium and surrounded by oedematous tissue. Both lesions were thought to be cerebral metastases of an unknown primary tumour.

In August 1988 the patient was admitted to hospital for palliative treatment of cerebral metastases and diagnostic search for the primary tumour. On examination, proximal and leg-accentuated flabby left hemiparesis and left hemidystaxia were found. Impairment of the vibration sensitivity of the left body half and left balance disorder were also diagnosed. The patient seemed to be mentally changed and inadequately euphoric. She was started on an anti-oedema treatment with steroids. At first her condition improved a bit. A second CAT scan of the brain showed a small diminution of the lesion in the parietal lobe.

A CAT scan of the thorax revealed two pulmonary lesions: one could be seen in the right lower field, the second, that was highly suspect of bronchial carcinoma, was found in the ventral part of the right lung near the aortic bend. As no other sign pointed towards another primary tumour, a primary bronchial carcinoma with cerebral metastases seemed most likely. Taking into consideration the border-compensated renal insufficiency of the patient, a palliative treatment consisting of radiotherapy of the cerebral metastases was agreed on. Shortly after the start of radiotherapy her condition deteriorated rapidly; she died in September 1988, four months after the diagnosis of metastases of an unknown primary tumour had been established. A post-mortem revealed pulmonary and cerebral metastases of renal cell carcinoma (RCC), i.e. metastases of her former renal cell carcinoma of 1976.

*Case 2.* In August 1977, a 68-year-old woman suffered from painless macrohaematuria. On clinical examination a palpable mass in the left flank was found, suspect of malignant renal tumour. A haemorrhage originating from the left ureteric ostium was endoscopically confirmed. Retrograde urogram showed a large space-occupying lesion in the middle and upper third of the left kidney. Renovasography and selective angiography confirmed the diagnosis of a huge, malignant left renal tumour. Cavography was without any evidence of a vena cava tumour thrombus.

After preoperative radiotherapy, left radical transperitoneal tumour nephrectomy and splenectomy were performed in September 1977.

Macroscopically a huge renal cell carcinoma of $7 \times 6 \times 4.5$ cm was found that had invaded the renal pelvis and the venous system near the renal hilum. Another tumour near the renal hilum turned out to be a metastasis in a hilar lymph node. Histologically the tumour represented a clear cell renal cell carcinoma with necroses and bleedings inside that invaded the venous system near the renal hilum and metastasized into hilar lymph nodes. The adrenal gland, the paraaortic lymph nodes and the spleen were free of tumour.

Postoperatively the patient made an uneventful recovery. However, as the tumour had spread to the hilar lymph nodes the patient received another radiotherapy of the left flank and the paraaortic lymph nodes about 3 weeks postoperatively, lasting 4 weeks. This was tolerated without any problems.

So far the follow-up at regular intervals has not revealed any tumour recurrence. In December 1989 the patient has been without any evidence of relapsing tumour for more than 12 years.

*Case 3.** A 58-year-old woman was transferred to our Department in September 1978, after she had been diagnosed at another hospital as having renal cell carcinoma of the left kidney with a solitary metastasis in the lower lobe of the right lung. In addition, renovasography was performed that clearly showed a huge malignant renal tumour in the upper pole of the left kidney. Cavography revealed a huge tumour thrombus in the renal vein. Preoperative chest X-ray confirmed the already mentioned pulmonary lesion in the right lower lobe (Fig. 1).

As after an extensive diagnostic search (by bone and CAT scan) no other metastases had been found, it was decided – on consultation with the thoracic surgeons – to perform left radical tumour nephrectomy. The single pulmonary metastasis was scheduled for resection in a second operation.

In October 1978, radical tumour nephrectomy combined with paraaortic lymphadenectomy was performed. Because of an excessive local tumour extension the spleen was also removed; intraoperatively it seemed that not every tumour-infected lymph node could be removed. The resected kidney was huge and macroscopically contained a renal cell carcinoma (6 cm in diameter) in the upper pole that had invaded the renal capsule and the renal vein with moulding a tumour thrombus. Histologically the tumour turned out to be a clear cell renal cell carcinoma that had infiltrated the renal capsule, the renal pelvis and the left adrenal gland and had spread to the hilar and paraaortic lymph nodes.

On the sixth postoperative day the patient developed a left-sided pleural empyema. Postoperative chest X-ray now revealed – in contrast to the preoperative one – an additional small right pulmonary metastasis just above the diaphragm (Fig. 2). Therefore, thoracotomy was cancelled.

The pleural empyema was drained and dissolved quite quickly. As otherwise no complication occurred, the patient was released home on the 28th postoperative day.

Due to a lack of convincing effects of chemo- and radiotherapy on renal cell carcinoma, the big tumour burden and the patient's devastating prognosis, no adjuvant therapy was considered. However, follow-up at three-month intervals demonstrated an astonishing development: three months postoperatively the

* Cases 3 and 4 are being published in a case report in the British Journal of Urology in 1990 [8]. As the present paper is not only about long-term survival and late recurrence but also about spontaneous regression, and as all three topics undoubtedly belong together, the authors deem it necessary to include these two cases here in order not to falsify or change the tenor of the review.

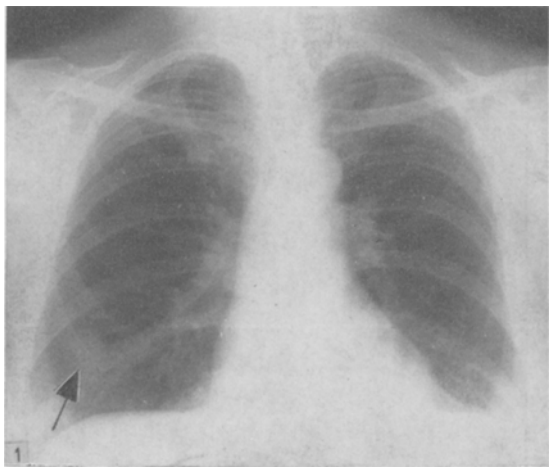

Fig. 1. *Case 3:* Preoperative chest X-ray of a 58-year-old woman with a single pulmonary metastasis of the right lower lobe

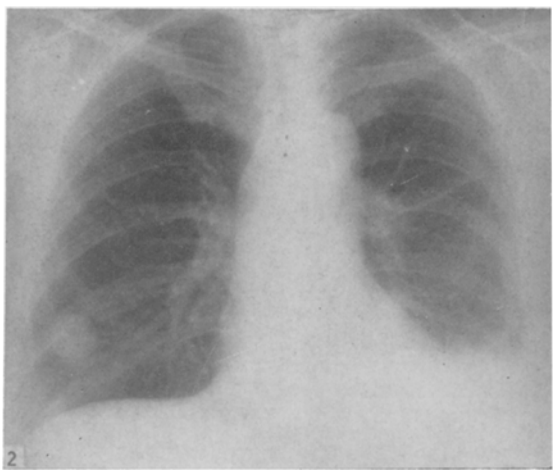

Fig. 2. *Case 3:* 20 days postoperatively a second pulmonary metastasis is clearly visible in the right phrenical angle

patient had gained 1 kg in weight; the first pulmonary metastasis, which had been 3 cm in diameter, had shrinked to 1.5 cm in size, the smaller second metastasis had vanished. Another three months later the patient was in a good condition, had gained another 5 kg, and the first pulmonary metastasis had also disappeared. The patient even wanted to start work again.

From October 1979 restaging was done half-yearly, from May 1983 yearly. In December 1989 the patient is still well and without any evidence of disease (Fig. 3).

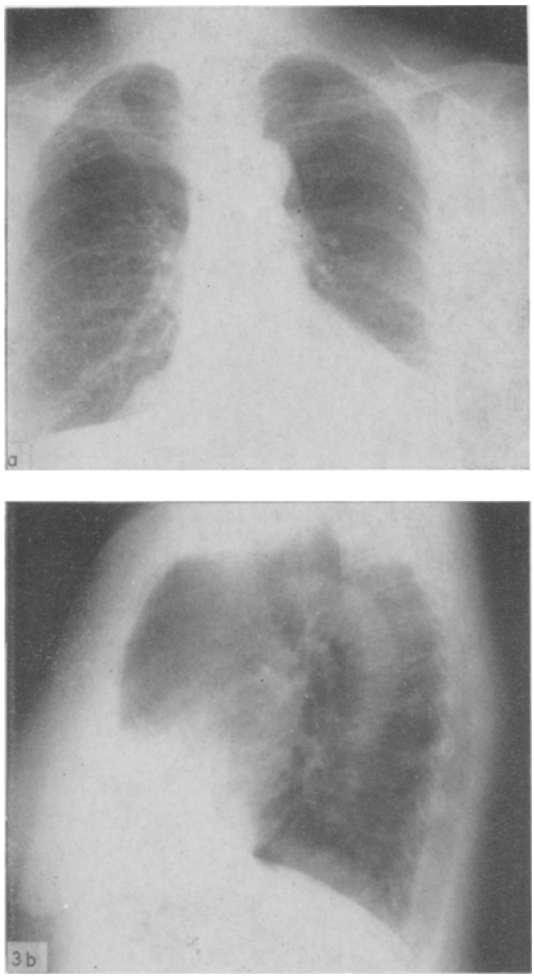


Fig. 3a, b. *Case 3:* Actual chest X-ray, 11 years after tumour nephrectomy: no evidence of pulmonary metastases

*Case 4.* In April 1984, a 45-year-old woman presented with permanent urge to cough. Chest X-ray revealed multiple metastases in both lungs (Fig. 4). Abdominal CAT scan revealed a left renal tumour 6 cm in diameter with enlarged paraaortic lymph nodes (Fig. 5).

According to this metastatic diagnosis, palliative hormonal treatment with the anti-oestrogen Tamoxifen (30 mg/day) for a period of 8 weeks was started in May 1984.

In June 1984 a clinically fit patient without any pathological breathing or palpable abdominal tumour or lymph nodes presented at our hospital. Restaging

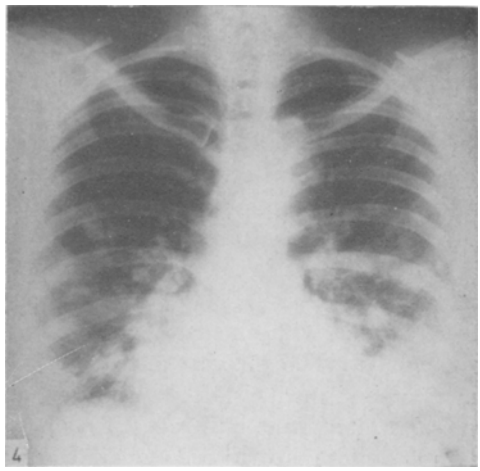

Fig. 4. *Case 4:* Preoperative chest X-ray of a 45-year-old woman: multiple pulmonary metastases on both sides

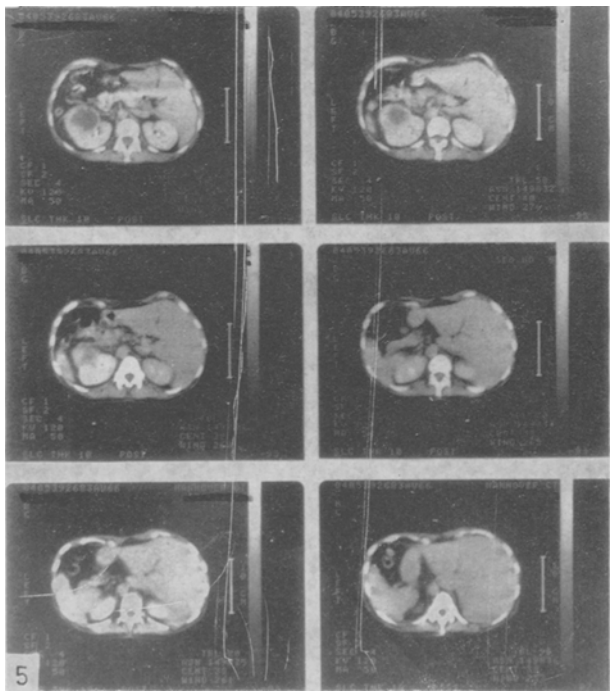

Fig. 5. *Case 4:* CAT scan of the abdomen: solid masses in the upper pole of the right kidney, combined with enlarged retroperitoneal lymph nodes

revealed a nearly complete regression of metastatic disease: a CAT scan of the thorax showed three residual pulmonary metastases in the right upper zone and another one in the left lower zone; chest X-ray only revealed two residual metastases in the right mid-zone. Abdominal ultrasound showed a decrease in size of the formerly enlarged lymph nodes. Therefore, after further investigation by IVU, renovasography, cavography and bone-scan, left transperitoneal radical tumour nephrectomy in combination with retroperitoneal lymphadenectomy was performed in July 1984.

Macroscopically a tumour 6 cm in diameter was found that seemed to have infiltrated the renal capsule and pelvis. Histological examination revealed a high grade (G3) renal cell carcinoma with extensive necroses and cicatrization that had infiltrated the renal pelvis. The macroscopically visible infiltration of the renal capsule could not be confirmed histologically; however, here an extensive cicatrization with regressive alterations and older bleedings could be seen. The hilar and paraaortic lymph nodes that had been enlarged on the abdominal CAT scan were histologically without any live tumour cells.

Postoperatively the patient made an uneventful recovery and was released home on the 11th postoperative day. She was kept on Tamoxifen 1 tablet t.d. (30 mg/day).

At follow-up in December 1984 she had improved a lot, only three little pulmonary metastases were left that were only seen on thoracic CAT scan (on normal chest X-ray they were not visible). On follow-up she has remained free of disease until now (December 1989) under a therapy of 10 mg Tamoxifen per day (Fig. 6).

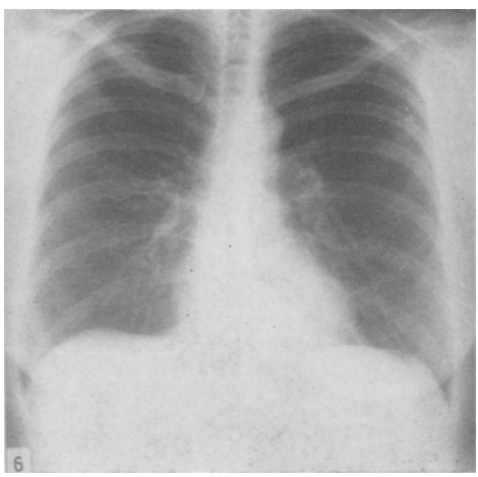


Fig. 6. *Case 4:* Latest chest X-ray: still no evidence of recurrent metastatic disease (e.g. pulmonary metastases)

## Discussion

Spontaneous regression of cancer has been a subject in the world literature since the beginning of this century [23]. The first case of spontaneous regression of metastatic renal cell carcinoma was described by Bumpus in 1928 [5]. Until recently some authors have doubted its existence. However, many authors have proved that spontaneous regression can occur. The tumour with the second most reported spontaneous regressions is renal cell carcinoma (after malignant melanoma) [26]. Katz and Schapira [16] even put renal cell carcinoma (RCC) in first place followed by neuroblastoma, melanoma and choriocarcinoma, in decreasing order of frequency. In 1977, Freed et al. [12] had collected 51 acceptable cases, inclusive 2 of their own. Only in one case had tumour regression occurred without nephrectomy, in two cases before nephrectomy and in 7 cases metastases occurred after nephrectomy and then regressed. In 4 cases regression occurred after nephrectomy and radiotherapy. In 45 cases spontaneous regression occurred in the lung, in only 6 cases had regression occurred elsewhere (3 bone, 1 intestines, 1 skin, 1 thigh). Histologically proven metastases had been documented in only 19 of the 51 cases, this is one third of all cases. Seven of these cases had a follow-up of 2 years or less, and the remaining 12 cases had remissions lasting from 3 to 21 years. Fairlamb [11] presents a similar list with 67 cases, the number of unreported cases may be much higher. The findings of Freed et al. [12] exactly reproduce Bloom's [1] definition of spontaneous regression:

"Spontaneous regression is a partial or complete disappearance of a malignant tumour in the absence of all treatment, or in the presence of therapy, which is considered inadequate to exert a significant influence on neoplastic disease, and therefore we do not consider spontaneous regression synonymous with cure."

One important question is: How often does spontaneous regression in metastatic renal cell carcinoma really occur?

In an estimation made by Bloom in 1973 [2] there were 3 acceptable cases of regression in a series of 1100 hypernephroma patients who had undergone nephrectomy (0.3%). Other estimates vary from 0.4 to 1%, this is 1 in 250 patients (0.4%) [22]. Already in 1947 Hultquist emphasized [14] that many areas of cortical renal scarring represent regressing or obsolescent renal cell carcinoma and that these self-healing renal cell carcinomas have been noted in association with spontaneous disappearance of metastases. So the real incidence of spontaneous regression should be much higher than 1%.

Another important question is: How long can spontaneous regression be expected to last? That spontaneous regression is not synonymous with cure has already been defined by Bloom [1] in 1964. Further clarification by Everson and Cole [10], in order to take account of the different developments of spontaneous regression in the world literature, reveals 6 distinct categories:

1. regression of the primary tumour;
2. regression of metastases with histologic confirmation;

3. regression of metastases without histologic confirmation;
4. regression of presumptive metastases judged only radiologically;
5. prolonged arrest;
6. delayed metastases or recurrence.

Bearing this clarification in mind, all of our 4 cases belong to at least one of the six categories and can therefore be called spontaneous regressions.

The last two categories are of particular interest to the urologist, as the biological activity of many genitourinary cancers, especially renal cell carcinoma, is notoriously unpredictable [16]. Not uncommonly, patients have delayed metastatic lesions from hypernephroma several years after a presumably curative nephrectomy. Our first case is a typical example. Here, more than 11 years after nephrectomy multiple metastases occurred in the brain and the lungs and the patient died 4 months after diagnosis. Other examples can be found in the literature [2, 9, 19, 28]. The questions are: What accounts for this variation in tumour activity? Is there a change in the tumour cells themselves causing increased virulence or is there a sudden breakdown in the host environment, permitting uncontrolled growth of tumour cells previously held in check? [16]

The last and probably most important question is: Why does spontaneous regression occur and where does it most commonly take place?

Although the concept of spontaneous regression of clinical cancer is tenable, the factors responsible for its occurrence remain conjectural. Aetiologic factors thought to be involved in spontaneous tumour regression include:

(a) host "walling-off" mechanisms with self healing;
(b) hormonally included changes;
(c) trauma (for example major surgery);
(d) infections and/or fever;
(e) alterations of the immune status [16].

Interesting is that 3 of these factors, that is infection, hormonally induced changes and altered immune status, appear to be present in the majority of reported cases. Indeed, Stephenson et al. [27] demonstrated $\geq 1$ of these 3 factors in 184 (82%) of their 224 patients.

Of particular interest in our case are the hormonally induced changes. Two different aspects play a role here of which one aspect is especially important because it has therapeutic consequences. The sex incidence of renal cell cancer is divided evenly between male and female patients $\leq 45$ years old. However, after menopause the relative female incidence decreases sharply so that the frequency in male patients becomes 2 to 3 times higher. The 5-year survival rate after nephrectomy is twice as great for men as for women. Although the range of ages for reported cases of spontaneous regression favours this postmenopausal group, the proportion of male patients demonstrating this phenomenon is disproportionately high (70%) [16]. Therefore the clinical effectiveness of progestational agents and androgens in treating patients with renal cell cancer has been studied extensively. Although initial reports on success with this mode of therapy quoted objective responses in approximately 16 per cent of the treated patients [3],

subsequent studies have failed to support these claims. Recent reports on the effectiveness of progestagens in cases of renal cell cancer show no statistical difference in survival between treated and untreated patients [4]. However, in our case the patient was started on hormonal therapy with the anti-oestrogen Tamoxifen, because her illness was too advanced to consider nephrectomy. Within a few weeks her pulmonary metastases had resolved as stated by Bloom [2]. After subsequent nephrectomy and continuous treatment with Tamoxifen 10 mg/day she has now remained free of disease for nearly 5 years. A similar case is reported by Kavoussi et al. [17], other positive cases by Bloom [3]. Therefore, there is a big chance that the presence or lack of oestrogen or progesterone receptors may predict a response to anti-oestrogen or progesterone therapy [26].

Interesting is that in most cases of spontaneous regression adjuvant radical nephrectomy had been performed before regression occurred. There are two hypotheses for this finding, both of them of immunological background:

1. Attempts at resection can disseminate tumour cells into blood vessels or lymphatics. This cell dissemination might result in a large tumour antigen load and perhaps stimulate a strong host antitumour response.

2. Simple debulking is the second possibility. The explanation might be that the antigen load of the primary tumour is too big for the body's immune system to be able to react. So nephrectomy would remove most of the antigen load and thus allow better use of the effector arms of the immune system [16].

Therefore most authors are in favour of nephrectomy [11, 13, 18, 19], especially if there is only a single metastasis [7, 17, 18]. Garfield [13] defines the role of adjunctive nephrectomy in patients with metastatic renal cell carcinoma as follows:

(i) nephrectomy may eliminate or prevent the source of fever and toxicity due to the primary tumour;

(ii) it may reverse hepatopathy;

(iii) secondary anaemia or erythrocytosis related to erythropoietin overproduction can be corrected;

(iv) removal of a large primary tumour may eliminate the source of pain and a potential source of haematuria;

(v) hypercalcaemia can be corrected;

(vi) removal of a large bulk of tumour eliminates the major source of a parathormone-like polypeptide;

(vii) an important factor, although rare, is the disappearance of metastases.

A final point is that in patients with histologically proven metastatic disease in the lymph nodes survival can be prolonged for a long time after nephrectomy, i.e. debulking, as our first three cases show. Without nephrectomy 80-90% of the patients with metastatic disease in the lymph nodes are dying within a year of diagnosis (follow-up of patients with lymph node metastases at our Department).

However, in recent years there have been voices against adjunctive nephrectomy [15, 20, 21, 22]. Since the incidence of regression of metastases had been

less than 1%, Middleton [20] calculated that the morbidity and mortality from nephrectomy in these patients are higher than the potential benefit and therefore concluded that nephrectomy for the sole purpose of achieving regression of metastases is not warranted in asymptomatic patients. The mortality of adjunctive nephrectomy under these circumstances ranges from 2 to 15%; most of the authors report 5% [6, 22, 25].

However, as the mortality is not much higher than in patients without metastases, if the patients are carefully selected we advocate adjunctive nephrectomy. Nevertheless, we think that if ever possible additional adjuvant therapy should be given, such as the application of biological response modifiers (e.g. interferons), with which the rate of spontaneous remissions can reach more than 20%. Interesting in this context is that there seems to be an organ specificity in the ability to cope with metastases [13, 16]. Out of 39 reported cases 37 represented regression of pulmonary metastases, and in some instances there was simultaneous regression of pulmonary metastases with progression of non-pulmonary metastases, e.g. in the bones or brain [13]. An explanation may be that pulmonary tissue, probably caused by constant exposure to foreign antigens, is especially rich in macrophages, lymphocytes and immunoglobulin IgA (immunological hypothesis) [16].

However, it is at present unknown which sort of adjuvant immunotherapy is best, despite extensive scientific research. We think that under the mentioned circumstances a therapeutic nihilism is not justified. In case of metastatic RCC we advocate radical tumour nephrectomy followed by an adjuvant therapy with interferons alone or in combination with interleukin-II.

Nevertheless, one has got to bear in mind what Montie and associates write: "The psychologic pressure imposed on a surgeon to perform an ablative procedure occasionally can be overwhelming. The desire by the physician and patient to do something must be judged in light of potential benefits from the operation and the operative mortality and morbidity. The psychological benefits may justify the risk undertaken but this should be recognized as such by the involved medical team" [22].

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