

Lung metastasectomy in patients with renal cell cancer (RCC). A 17-year experience in Parma Hospital

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Abstract. *Aim:* We aim to report the results of the curative, non-palliative, treatment of resection of lung metastases that are secondary to renal cell carcinoma (RCC). *Methods:* Between 1988 and 2004, a radical metastasectomy with curative purposes was performed in 20 (11 males and 9 females) patients with renal clear cell carcinoma (RCC) who had already undergone nephrectomy and subsequently metastasectomy of lung metastases. The mean age was 66,9 years (range 48-81 years). *Results:* the intraoperative mortality of patients undergoing surgical resection of lung metastases from RCC was 0%; 17 out of 20 patients returned at follow up; 9 patients died; the mean survival-time after nephrectomy was 64±42 months (range 7-132 months) and the mean survival-time after metastasectomy was 31±29 months (range 4-99 months); 4 out of 9 pts had pulmonary recurrence after surgery. 8 patients are still alive; the mean follow up after nephrectomy was 134±115 months (range 30-372 months) and 72±44 months (range 25-150 months) after metastasectomy. 1 out of 8 pts had a pulmonary recurrence that was treated by surgery. *Conclusions:* the radical resection of lung metastases is a safe and effective treatment in selected RCC patients. (www.actabiomedica.it)

Key words: Renal carcinoma, lung metastases, metastasectomy, survival

Introduction

The lung is one of the most frequently affected metastatic sites (second after the liver) in patients with renal clear cell carcinoma (RCC) (1, 2).

Twenty-five percent of the patients with RCC presented metastases at disease onset. Attempts to identify an effective medical treatment have provided poor results, thus surgery remains the most effective approach in the treatment of metastatic disease.

Patients with lung metastases were once considered untreatable, but nowadays they can benefit from surgery if they are selected according to the criteria proposed by Alexander and Haight in 1947 (3) and recently confirmed by Pastorino et al. (4). However, we should not forget that adjuvant systemic therapies with interleukin-2 (IL-2) with or without other cytokines or cellular therapy have shown good results in recently published clinical trials. Lipshultz et al. treat-

ed two metastatic RCC patients with IL-2 and INF- α who bearded their primary tumour in situ, reporting a complete regression of the lung metastases; subsequently, nephrectomy allowed a complete disease remission (5). However, the treatment of metastatic RCC still represents a widely debated issue. RCC has been treated with a wide spectrum of therapeutical approaches, which included experimental techniques and drugs, commonly referred to as biologic response modifiers (BRM). No effective chemotherapeutic or hormonal agents have been introduced so far. Adoptive immunotherapy and the administration of cytokines seem to represent the most effective treatment, although their efficacy and toxicity still need to be confirmed in large scale studies; moreover, more accurate patient selection is probably needed.

Here we report our experience concerning lung metastasectomy in patients with primary RCC during the last 17 years.

Patients and methods

Between January 1988 and December 2004, 20 patients with RCC underwent radical lung metastasectomy with curative purposes. Eleven (55%) patients were males mean age 69,2 years (range 57-81), and 9 (45%) patients were females, mean age 72 years (range 48-73).

All patients had already undergone primary tumour resection (left nephrectomy in 8 pts, right nephrectomy in 12 pts; one patient also underwent inferior vena cava resection because of neoplastic thrombosis and another patient underwent right ureterectomy). The patients are selected according to the criteria of Alexander and Haight (3): a) their primary tumour had already been completely removed; b) the histological type was known; c) there were no metastatic sites other than the lung; d) the operative risk was acceptable and the respiratory conditions were optimal.

The choice of the surgical access depended on the presence of uni- or bilateral metastases (ranged from 0,5 - 4 cmØ at CT-scan): for unilateral lesions thoracotomy was performed, whereas patients with bilateral metastases underwent a "clamshell incision"- which consists in a bilateral posterior-anterior thoracotomy

at the 5th inter-rib space –associated to a transversal sternotomy

Results

Twelve RCC patients had a single metastatic lung nodule; two patients had two unilateral nodules and one patient underwent two surgical operations; only one patient had three unilateral metastases; another patient had four unilateral metastases and underwent two surgical operations. Two RCC patients had five metastatic nodules (one of them underwent two operations and the other underwent three); only one patient had 15 unilateral nodules which were resected during a single surgical operation. Only one patient showed bilateral metastases (one nodule in the right lung and two in the left). The nodules were synchronous (9 patients) or metachronous.

The intraoperative mortality of the patients undergoing surgical resection of lung metastases from RCC was 0%; 17 out of 20 patients returned at follow up (Tables 1, 2). 9 patients died; the mean survival-time after nephrectomy was 64±42 months (range 7-132 months) and the mean survival-time after me-

Table 1. Clinical data and follow up after nephrectomy

| | Patients | Nephrectomy | s/ d | DFS N | Survival 5 / 10 years | |
|----|----------|-------------|------------|----------|--------------------------|-----|
| 1 | M.A. | 1/1990 | d: 9/1993 | 11 | 45 | */ |
| 2 | S.G. | 1/1988 | d: 5/1996 | 1 | / | 101 |
| 3 | M.I. | 1/1987 | s: 12/2004 | 67 | / | 216 |
| 4 | S.R. | 1/1990 | d: 4/1995 | 47 | / | 64 |
| 5 | Z.M. | 1/1974 | s: 12/2004 | 269 | / | 372 |
| 6 | P.A. | 1/1993 | s: 12/2004 | 51 | / | 144 |
| 7 | G.A. | 1/1998 | s: 12/2004 | 3 | / | 84 |
| 8 | G.E. | 4/1999 | d: 8/2001 | 3 | 28 | / |
| 9 | C.S. | 1/1994 | s: 12/2004 | 68 | / | 132 |
| 10 | B.G. | 10/1999 | d:10/2003 | 3 | 48 | / |
| 11 | B.G. | 1/1992 | d: 1/2003 | 98 | / | 133 |
| 12 | I.A. | 1/2000 | d: 8/2000 | 2 | 7 | / |
| 13 | PL. | 1/1997 | ? | 42 | / | 84 |
| 14 | V.S. | 1/1999 | d: 9/2002 | 31 | 45 | / |
| 15 | F.N. | 1/1992 | ? | 117 | / | 132 |
| 16 | D.G. | 1/1997 | ? | 58 | / | 72 |
| 17 | B.E. | 9/1999 | s: 12/2004 | 35 | 63 | / |
| 18 | N.I. | 7/2002 | s: 12/2004 | 1 | 29 | / |
| 19 | P.M. | 1/1993 | d: 6/2002 | 110 | / | 114 |
| 20 | T.T. | 7/2002 | s: 12/2004 | 5 | 29 | / |

Table 2. Clinical data and follow up after metastasectomy

| | Patients | Metastasectomy | Lung metastases | s / d | DFS M | Survival 5 / 10 years | |
|----|----------|----------------|-----------------|------------|-------|-----------------------|-----|
| 1 | M.A. | 12/1990 | 7 /1991 | d: 9/1993 | 7 | 34 | / |
| 2 | S.G. | 2/1988 | 5/1991 | d: 5/1996 | 39 | / | 99 |
| 3 | M.I. | 7/1992 | / | s: 12/2004 | / | / | 149 |
| 4 | S.R. | 11/1993 | / | d: 4/1995 | / | 17 | / |
| 5 | Z.M. | 5/1996 | / | s: 12/2004 | / | / | 103 |
| 6 | P.A. | 3/1997 | / | s: 12/2004 | / | / | 93 |
| 7 | G.A. | 4/1998 | 11/2002 | s: 12/2004 | 55 | / | 80 |
| 8 | G.E. | 7/1999 | / | d: 8/2001 | / | 25 | / |
| 9 | C.S. | 8/1999 | / | s: 12/2004 | / | / | 64 |
| 10 | B.G. | 1/2000 | 8/2002 | d:10/2003 | 31 | 45 | / |
| 11 | B.G. | 2/2000 | / | d: 1/2003 | / | 35 | / |
| 12 | I.A. | 3/2000 | / | d: 8/2000 | / | 5 | / |
| 13 | P.L. | 6/2000 | / | ? | / | 26 | ? |
| 14 | V.S. | 7/2001 | 4/2002 | d: 9/2002 | 39 | 13 | / |
| 15 | F.N. | 9/2001 | / | ? | / | 15 | ? |
| 16 | D.G. | 10/2001 | / | ? | / | 14 | ? |
| 17 | B.E. | 8/2002 | / | s: 12/2004 | / | 28 | / |
| 18 | N.I. | 8/2002 | / | s: 12/2004 | / | 28 | / |
| 19 | P.M. | 2/2002 | / | d: 6/2002 | / | 4 | / |
| 20 | T.T. | 12/2002 | / | s: 12/2004 | / | 25 | / |

Legend: S survival; D death; DFS N disease - free survival after nephrectomy; DFS M disease - free survival after metastasectomy

tastasectomy was 31 ± 29 months (range 4-99 months); 4 out of 9 pts had pulmonary recurrence after surgery. Eight patients are still alive (3 pts were lost at follow up); the mean follow up after nephrectomy was 134 ± 115 months (range: 30-372 months) and 72 ± 44 months (range 25-150 months) after metastasectomy. One out of 8 pts had a pulmonary recurrence treated with surgery (Figures 1, 2). Five patients were enrolled in experimental protocol for metastatic renal cell carcinoma and received adjuvant therapy with IL-2 and INF-alpha (4/5 pts are still alive).

Discussion and conclusions

Nowadays, in RCC patients with synchronous or metachronous lung metastases who have already undergone primary tumour resection, the best therapeutic results are obtained in selected cases by means of surgical resection of the metastatic nodules.

Csekeo et al. (6) surgically treated 57 patients, 32 with single metastases and 25 with multiple metastases:

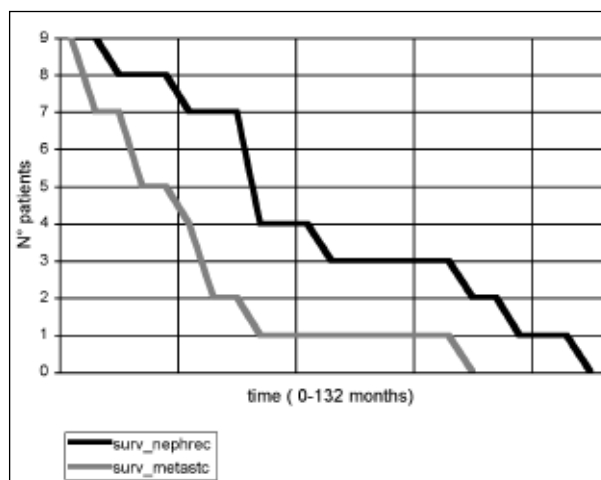


Figure 1. Global survival rate after nephrectomy and metastasectomy

they obtained a 5-year survival of 38%. Steinbach et al. (7) suggested that a multidisciplinary approach is required in patients with multiple metastases: given the high incidence of multiple metastases in a single patient, a cooperation between neurosurgeons, orthopaedics and thoracic surgeons is necessary. Okubo et

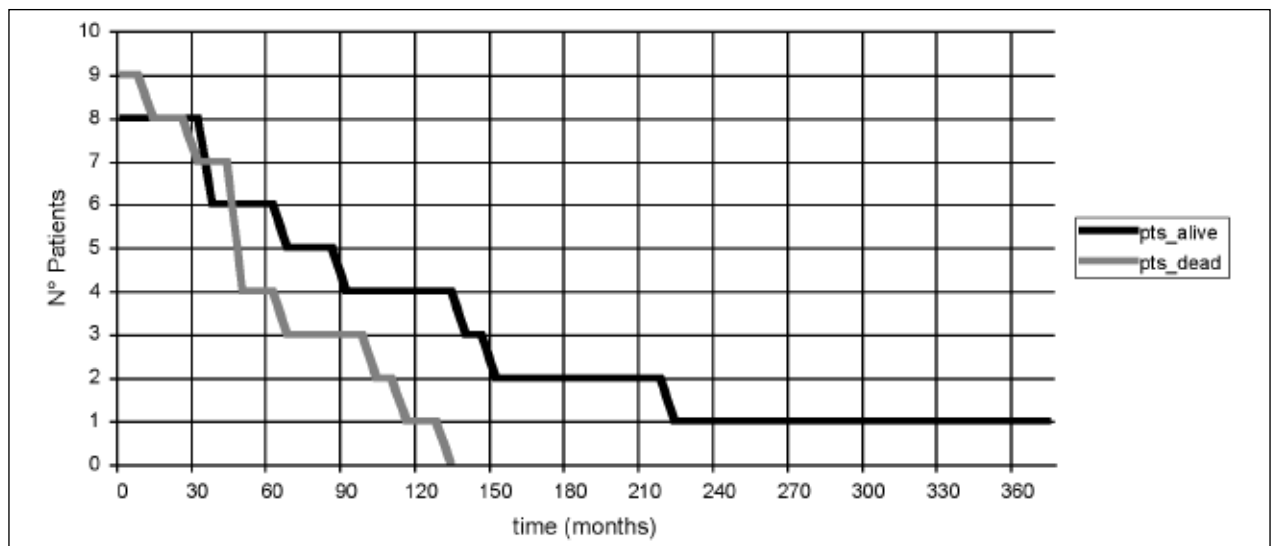


Figure 2. Global survival rate after nephrectomy (alive and dead patients)

al. (8) compared a surgical therapy with a medical approach (interferon): out of 29 patients, 18 underwent surgery and the remaining 11 received medical therapy: the 5-year survival in the two groups was 53% and 0%, respectively. Finally, Hosci et al. (9) suggested that surgery was effective in both patients with single and multiple lung nodules: they treated 17 patients (14 men and 3 women): one of them had a single metastasis, four had two nodules, two had three nodules, two had four nodules, one had seven nodules, one had eight nodules and six had more than 22 metastases.

Some Authors, such as Cozzoli et al. (10) distinguished two groups of patients surgically treated for lung metastases from RCC: out of 16 cases, six had synchronous metastases and 10 metachronous, with a median disease-free interval of about 23 months. The presence of synchronous lesions was an adverse prognostic factor (five out of six patients died or had a disease progression); better results were achieved in patients with metachronous lesions: one patient died, three had a disease progression, whereas six had overt signs of disease relapse (mean survival 43 months).

Fourquier et al. (11) showed that the complete resection of the metastatic lesions was an important prognostic factor; 50 patients were studied: 45 had a complete lung metastasis resection, one died and three had post-operative complications. The 5-year survival was

44%. Piltz et al. (12) reported a longer survival rate in patients undergoing lung metastases resection whose metastases had a diameter <4 cm without involvement of the lymph nodes (results obtained in 105 patients, with a 3-year survival of 54%, a 5-year survival of 40% and a 10-year survival of 33%).

The perspectives for a better cure for lung metastases rely on the effectiveness of systemic therapies in preventing their appearance. Presently systemic therapy plays a small role in the cure of both resectable and non-resectable metastases, but it cannot be excluded that future approaches may be more effective. Immunotherapy may be classified as either active or passive: in active therapy there is an attempt to induce an immune response towards tumour antigens, in patients bearing the tumour whereas, in the passive form, immunologically active substances with anti-tumour effects are administered. In the last decades, the techniques of recombinant DNA has led to the production of a large variety of purified lymphokines. The first was interferon- α . Studies on animal models demonstrated that combined therapy with IL-2 and IFN- α was able to reduce the number of liver metastases; in these studies, each cytokine was administered at a low dose, which was not effective if the cytokine was given alone, thus demonstrating a synergic anti-tumoral effect (13). Heinzer et al. (14) reported the effectiveness of

IL-2 in patients who could not undergo surgery, although several doubts are still present regarding the quality of life and the real effects of immunotherapy towards the risks brought about by its use.

In our experience, 20 patients were treated with curative purposes with a radical resection of pulmonary metastases; the nodules were single or multiple (up to 15), uni- or bilateral, synchronous (9 patients) or metachronous. Four out of five patients who received an adjuvant treatment with IL-2 and IFN- α , at present are still alive. The 5-year survival was 29% and the 10-year survival was 5%, with a longer survival rate in women than in men; the disease-free survival rate and the number of metastases did not significantly influence the prognosis.

In conclusion, the surgical treatment of lung metastases is nowadays the most effective and safe therapy in selected patients with RCC who have already undergone surgical resection of the primary tumour; the histological type must be known, and the patients' general conditions must be good enough to allow them to undergo surgery. Moreover, their residual respiratory function must be sufficient for a non-assisted post-operative respiration. It's clear that pulmonary metastatic disease relapse is a negative prognostic factor, in fact it was higher in the group of patients that died (4/9 pts) than in the group that survived (1/8 pt); also that the average survival rate after metastasectomy in the two groups we know was quite high, therefore we believe that a surgical approach is always suitable.

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