Strategies and outcomes in pulmonary and extrapulmonary metastases from renal cell cancer

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Abstract

Objective: Resected renal carcinoma related lung metastases (LM) are associated with higher survival rates, but surgery for extrapulmonary metastases affords good results too. Patients operated on for extrapulmonary metastases before thoracotomy are at high risk of death. The purpose of our analysis was to explore the surgical impact on the outcome of patients with such association.

Methods: We reviewed the data of 15 patients operated for LM and extrapulmonary metastases from 1984 to 2005. We studied demographic and clinical characteristics, surgical results and pathological staging of the primary tumour and LM in search of prognostic factors.

Results: Nephrectomy and metastasectomies were synchronous in only one patient. For the others, mean time interval between nephrectomy and surgery for LM was 74.2 months (range 19—228). Metastases were resected synchronously in two patients and metachronously in 13 of them (mean time interval: 28 months). Five-year survival of this group was 32%, median value of 18 months. The prognosis was better when the resected extrapulmonary metastases were located in the perirenal (pancreas, adrenal gland) or intrathoracic structures (lymph nodes, diaphragm) than in distant visceral organs (brain, bone, thyroid gland). The lymphatic drainage for these structures connects with the thoracic duct in a similar manner as kidneys do.

Conclusion: Surgery for lung and extrapulmonary renal cell cancer-related metastases provides favourable results and is indicated when complete resection can be achieved. The role of the lymphatic system must be explored by further investigations.

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Keywords: Renal carcinoma; Lung metastases; Extrapulmonary metastases; Lymph drainage; Thoracic duct; Surgery

1. Introduction

Lungs are the most common sites of metastases in renal cell carcinoma (RCC) patients [1]. Pulmonary metastasectomies are associated with higher survival rates, and results are better when compared to other anatomic locations [2]. The number of resected lung metastases (LM) has little influence on survival when the resection is complete [2]. Surgery for extrapulmonary metastases can also afford a good outcome, the number of metastatic sites rather than anatomi cal location being associated with poorer prognosis [3]. Patients operated on for extrapulmonary RCC-related metastases before thoracotomy are at higher risk of death [4], but completely resected extrathoracic metastases do not appear to preclude pulmonary metastasectomy [5]. The purpose of our analysis was to explore the surgical impact on the outcome of patients with LM, previously or synchronously operated on for extrapulmonary metastases.

2. Patients and methods

From January 1984 to December 2005, 70 consecutive RCC patients underwent thoracic surgery in three French centres (Georges Pompidou European Hospital, Tenon Hospital, and Boisguillaume Surgery Centre). All patients had been previously operated on by radical nephrectomy. The LMs were unilateral in 49 patients (70%) and bilateral in 21 cases (30%). Median survival was 34.4% for the entire cohort, with a median of 35 months. The LMs were the only metastases in 55 patients (78.6%), and were associated with extrapulmonary metastases in 15 patients (21.4%): the second group was the cohort of interest, analysed in an exploratory manner. The local Institutional Review Board waived obtaining patients’ consent for this retrospective study. We analysed demographic and clinical characteristics, surgical results, and data derived from the pathological staging of the primary renal tumour and LMs as specified by the American Joint Committee of Cancer.
Clinical information was obtained from the hospital case records. Pathology reports concerning the nephrectomy were obtained from the corresponding urological centres. Follow-up information was recorded either in the hospital case records (for censored patients) or in a questionnaire completed by the local chest physician, general practitioner or from death certificates. The overall survival was the main endpoint defined as the time interval between the date of LM surgery and death, or the last follow-up for living patients. No loss of follow-up was registered. Actuarial survival probabilities were estimated using Kaplan–Meier method. Statistical comparisons were made using an unstratified log-rank test. A p value less than 0.05 was considered statistically significant. All estimated p values were two-sided. The statistical software used for the analysis was SEM (AntiCancer Centre Jean Perrin, Clermont Ferrand, France) [7].

3. Results

There were 13 [87% (95% CI 60–98%)] men and two [13% (95% CI 2–41%)] women. These 15 patients (Table 1) were operated on between 1994 and 2005, the median age was 61 years (range 46–71). Lung metastases were right-sided in eight patients [53% (95% CI 27–79%)], left-sided in six patients [40% (95% CI 16–68%)] and bilateral in one patient [7% (95% CI 0.2–32%)]. The median number of lung metastases was 1 (range 1–8) and the median size was 1.5 cm (range 0.2–6 cm). More than half of patients [60% (95% CI 32–84%)] had a pulmonary wedge resection and 33% (95% CI 12–62%) a lobectomy. A combined wedge resection and lobectomy was performed in one patient only. Eighty percent (95% CI 52–96%) of patients were considered as pN0 (no hilar or mediastinal lymph nodes involvement). There were no significant statistical differences between the type of thoracic surgery according to sex, number of lung metastases, side and type of adjuvant treatment. Significant differences were observed according to age (more lobectomies for older patients, \( p = 0.001 \)) and borderline results were found according to pathological lymph nodes status (more lobectomies for N or N2 patients, \( p = 0.06 \)).

The patient with bilateral LM had a synchronous RCC: the other involved organ was the ipsilateral adrenal gland. This patient (patient no. 3) survived 16 months.

For the 14 other patients, disease-free survival was estimated as the time interval between nephrectomy and surgery for LM ranged from 19 to 228 months. There was no RCC and synchronous LMs. Other metastatic sites were: pancreas \( n = 5 \), adrenal gland \( n = 3 \), brain \( n = 3 \), diaphragm \( n = 3 \), bone \( n = 2 \), thyroid gland \( n = 1 \), mediastinal lymph nodes \( n = 1 \); (thyroid, diaphragm and pancreatic metastases in one patient and brain, diaphragm and pancreatic metastases in another one), (Table 2).

LMs and extrapulmonary metastases were synchronously treated in two patients (bone \( n = 1 \) and diaphragm \( n = 1 \)). For the remaining 13 patients, time intervals between the

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year of diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Side</th>
<th>Number of metastases</th>
<th>Type of resection</th>
<th>Size (cm)</th>
<th>N</th>
<th>Adjuvant treatment</th>
<th>Status</th>
<th>Length of survival (months)</th>
</tr>
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<tr>
<td>1</td>
<td>1994</td>
<td>F</td>
<td>62</td>
<td>L</td>
<td>2</td>
<td>Wedge × 2 (both lobes)</td>
<td>2.0</td>
<td>0</td>
<td></td>
<td>Dead</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>1994</td>
<td>M</td>
<td>64</td>
<td>R</td>
<td>1</td>
<td>Wedge</td>
<td>0.5</td>
<td>0</td>
<td>CT</td>
<td>Dead</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>1994</td>
<td>M</td>
<td>46</td>
<td>L × R</td>
<td>7</td>
<td>Wedge</td>
<td>3.5</td>
<td>0</td>
<td>IT</td>
<td>Dead</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>1995</td>
<td>M</td>
<td>57</td>
<td>R</td>
<td>1</td>
<td>Wedge</td>
<td>4.7</td>
<td>0</td>
<td></td>
<td>Dead</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>1996</td>
<td>M</td>
<td>71</td>
<td>R</td>
<td>1</td>
<td>Lobectomy</td>
<td>4.0</td>
<td>0</td>
<td></td>
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<td>25</td>
</tr>
<tr>
<td>6</td>
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<td>69</td>
<td>R</td>
<td>8</td>
<td>Wedge × 3 (lobes)</td>
<td>0.7</td>
<td>0</td>
<td></td>
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<td>109</td>
</tr>
<tr>
<td>7</td>
<td>1999</td>
<td>M</td>
<td>66</td>
<td>R</td>
<td>2</td>
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<tr>
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<td>51</td>
<td>L</td>
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<td>Wedge × 2 (both lobes)</td>
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<td></td>
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</tr>
<tr>
<td>9</td>
<td>2000</td>
<td>M</td>
<td>61</td>
<td>R</td>
<td>1</td>
<td>Lobectomy</td>
<td>2.4</td>
<td>N1</td>
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<tr>
<td>10</td>
<td>2001</td>
<td>M</td>
<td>63</td>
<td>R</td>
<td>3</td>
<td>Inferior lobectomy + wedge</td>
<td>1.3</td>
<td>N0</td>
<td>IT</td>
<td>Alive</td>
<td>61</td>
</tr>
<tr>
<td>11</td>
<td>2002</td>
<td>M</td>
<td>56</td>
<td>R</td>
<td>6</td>
<td>Wedge × 2 (both lobes)</td>
<td>2.0</td>
<td>0</td>
<td></td>
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<td>1</td>
<td>Inferior lobectomy</td>
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<td>N1</td>
<td>NZ</td>
<td>Alive</td>
<td>46</td>
</tr>
<tr>
<td>13</td>
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<td>F</td>
<td>59</td>
<td>L</td>
<td>1</td>
<td>Lobectomy</td>
<td>2.5</td>
<td>N1</td>
<td>NZ</td>
<td>Dead</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
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<td>L</td>
<td>1</td>
<td>Wedge (upper lobe)</td>
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<td></td>
<td>Alive</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>2005</td>
<td>M</td>
<td>70</td>
<td>L</td>
<td>1</td>
<td>Inferior lobectomy</td>
<td>6.0</td>
<td>N0</td>
<td>CT</td>
<td>Alive</td>
<td>12</td>
</tr>
</tbody>
</table>

F: Female; M: male; L: left; R: right; IT: immunotherapy; CT: chemotherapy; RT: radiation therapy; patient 11: presented visceral pleural involvement; patient 14: pericardium \( n = 1 \) and diaphragm \( n = 2 \) metastases discovered during thoracotomy were also resected; N1: intrapulmonary LN involvement; N2 mediastinal LN involvement.

* Smaller LM were not measured (evaluable but non measurable lesions).
extrapulmonary surgery and LM resection ranged between 2 and 108 months. Two patients underwent several metastasectomies. The interval between the last extrathoracic and LM surgery was 9 and 12 months, respectively. In two patients, a past history of partial nephrectomy for a contralateral RCC was described.

Pathology reports of the initial nephrectomy and LM surgery are shown in Fig. 1. Pathological staging was as follows: pT1 n = 2, pT2 n = 5, pT3b n = 5, in 12 patients with no regional LN involvement, and pT2 n = 2, pT3a n = 1 in three patients with regional LN involvement. There was a single LM in eight patients and multiple LMs in seven of them.

Five-year overall survival was 32%, with a median value of 18 months. The outcome seemed better for those patients with extrapulmonary metastases located in the perirenal region (pancreas n = 3, adrenal gland n = 3) or within thoracic structures (lymph nodes n = 1 and diaphragm n = 1), than for patients with metastases in distant organs (brain n = 3, bone n = 2, thyroid n = 1 and contralateral lung n = 1), (Fig. 2).

Among the latter, four patients with metastases in distant organs without perirenal metastases (patients 4, 7, 9 and 13) had their primary tumour limited to the kidney (pT1 and pT2, N0), (Fig. 1).

4. Discussion

Surgery of LMs related to a primary RCC is safe and curative in more than one third of patients, the most important predictive factor for a long-term survival being the completeness of resection [8–10]. The number of resected metastases is also an important factor of mortality [4,8–10], but Murthy et al. [5] demonstrated that both factors are
linked, the number of LMs being inversely related to the ability to achieve complete resection. When the resection is complete, consecutive LMs resection in the same patient is associated with a better survival [2]. Extrapulmonary metastases may benefit from surgery, the presence of multiple visceral metastases including LMs is not a contraindication [5]. This is supported by our results that are as good as those obtained after surgery for LM only. Actually, there is no formal explanation for this phenomenon. It is probably due to ‘a particular biologic behaviour’ of these multivisceral metastases. Completeness of resection remains the main prognostic factor and surgery should not be performed when a complete resection seems impossible to obtain.

No long-term survivors are expected after LMs surgery when retroperitoneal LN involvement is present at the time of nephrectomy [9]. Pantuck et al. [11] report that patients operated on for RCC with regional LN metastases and LMs had significantly lower survival rates than patients presenting either with regional LN involvement or LMs only. Our cohort was too small to be supportive (three patients with pN+), but most eligible patients for LMs surgery are probably those with no retroperitoneal LN involvement.

Lung metastases may have a special place in the extrapulmonary RCC-related metastatic pattern [12,13]. Saitoh et al. [13] observed that LMs alone are less frequent (32%) than LMs associated with multiple visceral involvement (76%). They hypothesised that LMs are the consequence of a one-step process, tumour cells directly disseminating from the primary lesion, the other metastases being the result of a multistep process (‘cascade’) and do not originate from the primary tumour but from the LMs. This hypothesis does not appear tenable with LMs occurring late during the RCC natural history, after other organ involvement, as was the case for some of our patients.

Lung metastases share the same poor outcome as RCC invading the venous system [6]. Tumour cells are hypothesised to disseminate into the blood stream by a haematogenous spread. The venous involvement may concern the inferior venous caval or renal vein(s) [6,14], and also the venous system of the renal sinus [15]. However, radical nephrectomy and complete removal of the venous extension provides cure rates approaching that of patients with stage I AJCC [14]. The venous involvement does not correlate with a higher LMs frequency.

Haematogenous spread mechanism resulting in extrapulmonary metastases was discussed by Sellner et al. [16]. They observed a discrepancy between a relative higher frequency of multiple pancreatic metastases and the absence of metastasis to the other organs among patients with RCC-related pancreatic metastases. It was suggested that this unique behaviour, which a haematogenous mechanism cannot explain, might be most likely based on a particular tumour biology. We observed such presentation in one of our patients that underwent three successive pancreatic surgeries. We also observed two patients that were operated for pancreatic metastases, synchronous with thyroid metastases in one case, or brain and diaphragm metastases in the other case.

To explain pancreatic metastases, Kassabian et al. [17] and Uemura et al. [18] have suggested a local lymphogenous or venous spread mechanism. The venous spread is supposed to occur along the collateral veins of a hypervascular tumour, associated or not with renal venous thrombosis [19]. A longer disease-free interval between nephrectomy and pancreatic surgery, and the absence of renal venous obstruction in our patients does not support this mechanism of pancreatic involvement. A local lymphogenous spread to the pancreas is supposed to occur by a retrograde lymph back-flow, secondary to the retroperitoneal LNs involvement [17]. Its absence in our patients does not support the lymphogenous hypothesis, but we still believe that a retrograde lymph back-flow is the most attractive hypothesis.

Renal lymphatic drainage is very important [20], anatomical studies demonstrated that kidneys and pancreas share common para-aortic LN territories [21,22]. These studies...
showed that lymph from both organs can flow into the origin of the thoracic duct (TD), sometimes without crossing any LN, thus permitting the cancer cells to be drained into the superior vena cava via the TD. Tumour cells reflux from the TD, though insufficient lymphatic valves have been reported as the most conceivable mechanism explaining hilar and mediastinal LN involvement without LMs occurring after long disease-free intervals [23,24]. We support the hypothesis that pancreatic metastases are explained by that retrograde TD lymphatic reflux. It explains the occurrence of multiple and iterative pancreatic metastases (Fig. 3), which we observed in our cohort, that are not infrequent [25]. It also explains why metastases may occur in other loco-regional organs (adrenal glands or contralateral kidney), and why pancreatic and adrenal glands metastases are not necessarily ipsilateral.

However, the longer disease-free intervals that we observed are commonly reported in surgical literature and remain unclear as mechanism. Dormant cells in G0 phase of the cycle could be sequestered within the TD insufficient lymphatic vessels explaining the bi-directional TD lymphatic drainage.

To conclude, surgery for RCC-related metastases may provide favourable long-term results and should not be contraindicated for recurrent disease when complete resection may be achieved. Forthcoming studies should analyse the role of the lymphatic system and the biology of metastatic cells in order to clarify the pattern of spread of RCC metastases.

References


