

## Case Reports

# Metastatic Non-Small-Cell Lung Carcinoma Successfully Treated with Pre-operative Chemotherapy and Bilateral Adrenalectomy

Alberto Muñoz<sup>1</sup>, Guillermo López-Vivanco<sup>1</sup>, Joan-Manel Mañé<sup>1</sup>, Ricardo Fernández<sup>1</sup>,  
Javier Díaz-Aguirregoitia<sup>2</sup>, Mónica Saiz<sup>3</sup> and Ramón Barceló<sup>1</sup>

<sup>1</sup>Department of Medical Oncology, <sup>2</sup>Department of Surgery, Unit of Endocrine Surgery and <sup>3</sup>Department of Pathology, Hospital de Cruces, Osakidetza, Basque Country, Spain

Received December 18, 2005; accepted July 15, 2006; published online October 27, 2006

Metastatic non-small-cell lung cancer is a common condition with a dismal prognosis. Although palliative chemotherapy improves survival and quality of life, nearly all patients die of progressive disease. Metastatic involvement of adrenal glands is not rare, but usually reflects widespread dissemination. Selected patients with single adrenal metastasis may be cured with surgery, although the level of evidence comes from single cases reports and short retrospective series. Here we report a patient with bilateral adrenal metastases from previously resected non-small-cell lung cancer, who remains free of disease four years after pre-operative chemotherapy and bilateral adrenalectomy.

*Key words: non-small-cell lung carcinoma – chemotherapy – surgery – adrenalectomy*

## INTRODUCTION

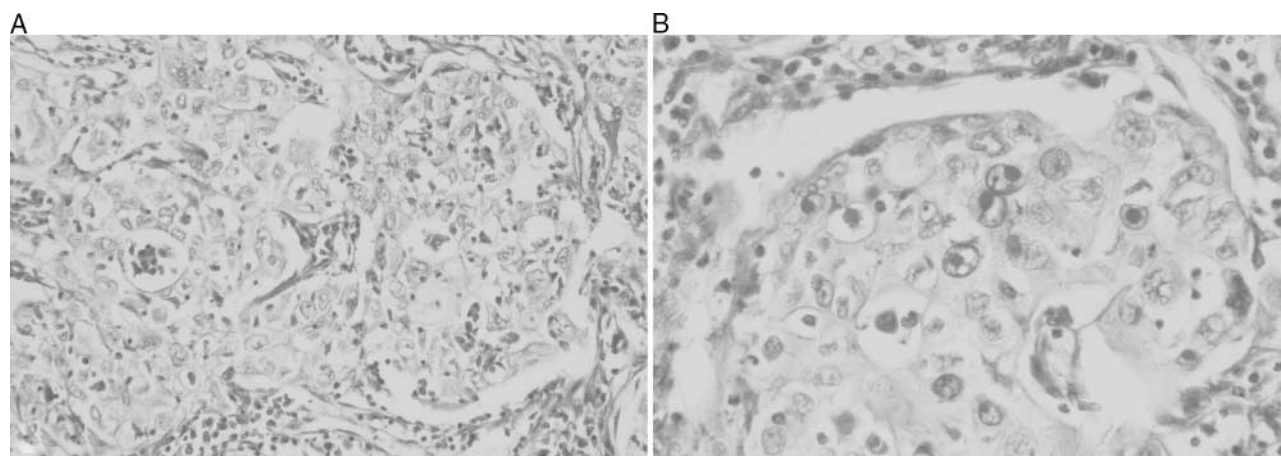
Metastatic non-small-cell lung cancer (NSCLC) is considered an incurable disease in most cases. In this setting, only salvage resection of single brain metastases may be judged as a standard surgery in selected patients with controlled primary tumour (1,2). Lung carcinoma commonly metastasizes to adrenal glands (3,4). Although adrenalectomy has been reported in several single cases and small series of selected patients with metastatic NSCLC, the precise role of this approach remains controversial (5). Bilateral involvement of adrenal glands is not uncommon, but usually is associated with diffuse systemic spread. In a computerized Medline search in English medical literature about adrenalectomy for metastatic lung cancer, we have retrieved only two cases of bilateral involvement of adrenal glands surgically removed (6,7). We report here another highly selected patient successfully treated with pre-operative chemotherapy followed by adrenalectomy for metastases to both adrenal glands.

## CASE REPORT

A 54-year-old Caucasian man complained of right chest pain and dry cough during the last 4 months. He was an active smoker of 20 cigarettes per day and he had no relevant medical history. Thorax and abdomen CT scan showed a peripheral mass of 3 × 4 cm in right upper pulmonary lobe with chest wall invasion. Bronchoscopy was normal and a CT-guided biopsy was performed revealing large cell carcinoma. On December 1999, right upper lobectomy with chest wall en block resection was performed. The histopathological study showed a poorly differentiated adenocarcinoma (Fig. 1) measuring 8 × 5 cm with invasion of parietal pleura, ribs and muscle, and bronchial and chest wall margins free of disease: stage IIB (pT3pN0).

Three months later he noted pain in the right hypochondrium and a CT scan showed bilateral enlargement of adrenal glands (Fig. 2), with two masses of 7 cm in the right side and 5 × 2 cm in the left side, without any other evidence of disease. A CT scan-guided biopsy of the right adrenal mass was performed demonstrating infiltration of large cell carcinoma. In April 2000, he started chemotherapy with cisplatin 100 mg/m<sup>2</sup> on day 1 and gemcitabine 1200 mg/m<sup>2</sup> on days 1 and 8, every 21 days. After three courses of chemotherapy he achieved a partial response and

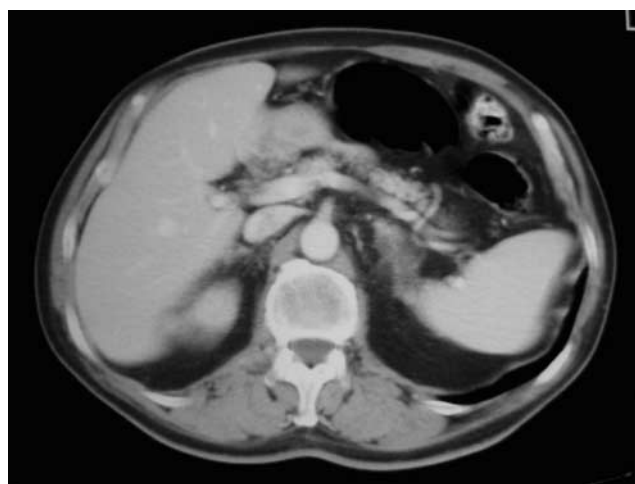
For reprints and all correspondence: Alberto Muñoz, Plaza de Cruces s/n, 48903 Barakaldo, Basque Country, Spain.  
E-mail: amunoz@hcru.osakidetza.net



**Figure 1.** Low power view of intraalveolar tumor growth (A). High power view of poorly differentiated adenocarcinoma filling alveolar space. Notice PAS positive droplets (B). Please note that a colour version of this figure is available as supplementary data at <http://ijco.oxfordjournals.org>.



**Figure 2.** Gross metastatic involvement of both adrenal glands before neoadjuvant chemotherapy.



**Figure 3.** Abdominal CT scan after six chemotherapy cycles showing near complete response. Notice major shrinking of both adrenals and density changes only in the left one.

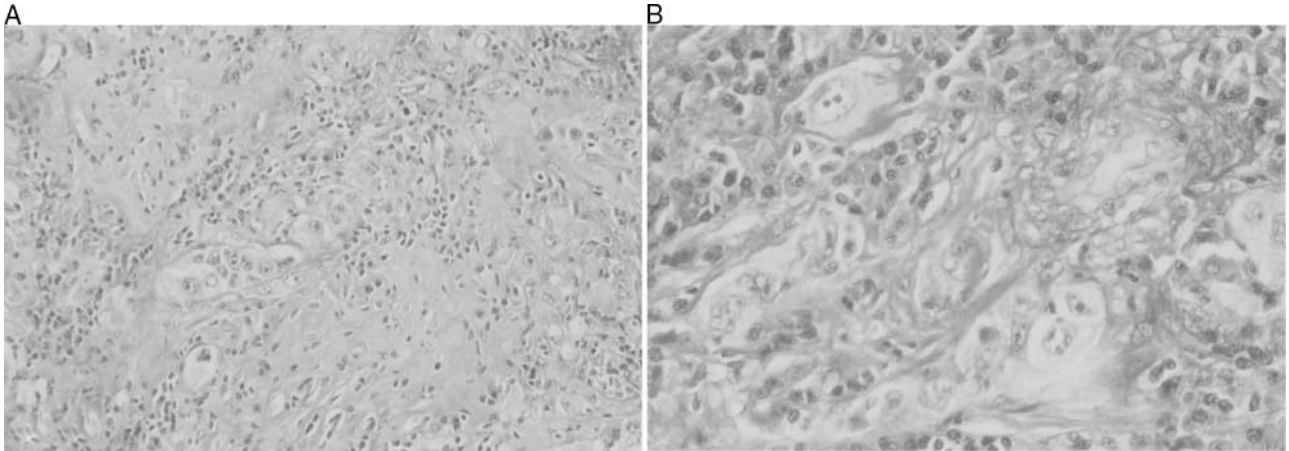
a CT scan done after the sixth cycle showed radiological complete response (Fig. 3). In October 2000, bilateral subcostal laparotomy was performed. At surgery, both adrenal glands seemed to be fibrous, with thrombosis of their veins and the spleen surface looked granular. Bilateral adrenalectomy and splenectomy was accomplished with no post-operative complications. Immediately after surgery, hormonal replacement was started with daily hydrocortisone and fludrocortisone. Pathological examination of the adrenals revealed hemorrhagic fibrosis in both glands and microscopic foci of large cell carcinoma in only the left gland (Fig. 4). Splenic parenchyma was within normal limits.

After surgery recovery, two more cycles of cisplatin and gemcitabine with the same schedule were administered. Treatment was finished on February 2001, the patient has been followed up every three months by physical exam, biochemistry, tumour markers and CT scans, and to date he remains free of disease.

## DISCUSSION

Treatment of choice for patients with stage IV lung carcinoma and good performance status is palliative chemotherapy. Although chemotherapy improves survival and quality of life in these patients (8), virtually all patients will die of progressive disease. Some patients with stage IV NSCLC have a solitary metastasis as the only sign of advanced disease, creating a medical dilemma for clinicians. For these patients a surgical approach might be considered but, unfortunately, only a resection of single brain metastases (2) has clearly demonstrated in randomized trials to have any impact on survival.

Adrenal glands are one of the most frequent sites of spread from NSCLC. In some necropsy series around one-third of patients had metastases in adrenal glands (4). Usually, adrenal metastases are associated with more extensive disease, but it is not exceptional to first appear as a single synchronous or metachronous metastasis. Some



**Figure 4.** Low power view of left adrenal and tumor tissue. Notice dense lymphoid infiltration of both (A). Isolated small nests of tumor cells in the midst of inflammation and fibrosis (B). Please note that a colour version of this figure is available as supplementary data at <http://jjco.oxfordjournals.org>.

authors have hypothesized that adrenal involvement in NSCLC could be as a consequence of both lymphogenous and hematogenous dissemination (9). This theoretical lymphatic route of spreading may reaffirm the role of surgery for isolated adrenal metastasis, on the assumption that it was a regional disease. Moreover, both open and laparoscopic adrenalectomy have become safe techniques in the hands of expert surgeons (7,10).

Currently, less than one hundred unilateral adrenalectomies for metastatic NSCLC have been published in English language medical literature. Most of them have been reported as single cases, although some reference institutions have communicated their cumulative experience with a number of patients (5,10,11–18). Based on the available information, it is very difficult to extract true conclusions and even more to establish general recommendations for the management of these patients. Probably, there are selection and publication biases in favour of patients with a good outcome. It may explain that patients of large series have generally shorter survival than those reported as single cases (5). Mediastinal nodal involvement and a short disease-free interval seem to be important prognostic factors and may predict poor outcome after adrenalectomy (5,10). However, the majority of authors recommend adjuvant chemotherapy after surgery, with an attempt to reduce or delay relapses, despite being, until recent times, an unproven treatment for completely resected NSCLC (19). Perhaps the most important conclusion is that some patients may survive a long time without relapse after resection of isolated adrenal metastases. For bilateral adrenal involvement the lack of evidence for surgery is more obvious, with only two cases reported so far. The first patient (6), as in our case, with a favourable long-term relapse-free survival (more than 9 years), but the other one with a worse prognosis died 13 months after surgery (7).

The alternative to surgery for patients with metastatic NSCLC is systemic chemotherapy. Combination chemotherapy with a platinum compound and a new agent is considered now the standard of care for patients with advanced-stage

NSCLC (20). However, median overall survival of NSCLC patients treated with chemotherapy is about 8 months nowadays, with less than 10% alive at two years. Taking into account that chemotherapy may play an important role in patients with adrenal metastases, as a palliative alternative or adjuvant to surgery, the neoadjuvant approach can be reasonable in particular cases. Patients with synchronous metastases and those with large or bilateral involvement could be treated with chemotherapy after an extensive radiological staging and, in case of response, salvage surgery may be a realistic option.

In our patient, rapid progression after lung surgery with large, bilateral and symptomatic involvement of the adrenal glands invited us to propose systemic chemotherapy. Because of the excellent response to chemotherapy without widespread dissemination and no nodal disease at resection, salvage surgery with two cycles more with adjuvant intent was offered.

With this case report we want to point out that, in selected cases, surgery may change the natural history of some patients with ill-starred prognosis with conventional treatments. However, we do not think that this approach may be considered a standard option for all patients with adrenal metastasis. It could be considered as a highly selected individualized approach based on age, co-morbidity, performance status, disease-free interval since lung surgery, prognostic factors derived from pathological stage of lung carcinoma, previous experience of the surgeon and patient's wishes. Multidisciplinary evaluation by expert surgeons and oncologists seems crucial in the management of selected patients with potentially resectable stage IV NSCLC, such as this one.

## References

1. Wronski M, Arbit E, Burt M, Galicich JH. Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. *J Neurosurg* 1995;83:605–16.

2. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494–500.
3. Abrams HL, Sprio R, Goldestein N. Metastases in carcinoma: analysis of 1000 autopsied cases. *Cancer* 1950;3:74–85.
4. Marabella P, Takita H. Adenocarcinoma of the lung: clinico-pathological study. *J Surg Oncol* 1975;7:205–12.
5. Beitler AL, Urschel JD, Velagapudi SRC, Takita H. Surgical management of adrenal metastases from lung cancer. *J Surg Oncol* 1998;69:54–57.
6. Urschel JD, Finley RK, Takita H. Long-term survival after bilateral adrenalectomy for metastatic lung cancer: a case report. *Chest* 1997;112:848–50.
7. Hasan R, Harold KL, Matthews BD, Kercher KW, Sing RF, Heniford BT. Outcomes for laparoscopic bilateral adrenalectomy. *J Laparoendosc Adv Surg Tech A* 2002;12:233–6.
8. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995;311:899–909.
9. Karolyi P. Do adrenal metastases from lung cancer develop by lymphogenous or hematogenous route? *J Surg Oncol* 1990;43:154–6.
10. Sarela AI, Murphy I, Coit DG, Conlon KC. Metastasis to the adrenal gland: the emerging role of laparoscopic surgery. *Ann Surg Oncol* 2003;10:1191–6.
11. Abdel-Raheem MM, Potti A, Becker WK, Saberi A, Mehdi SA. Late adrenal metastasis in operable non-small-cell lung carcinoma. *Am J Clin Oncol* 2002;25:81–3.
12. Bretcha-Boix P, Rami-Porta R, Mateu-Navarro M, Hoyuela-Alonso C, Marco-Molina C. Surgical treatment of lung cancer with adrenal metastasis. *Lung Cancer* 2000;27:101–5.
13. Porte HL, Roumilhac D, Graziana JP, Eraldi L, Cordonier C, Puech P, et al. Adrenalectomy for a solitary adrenal metastasis from lung cancer. *Ann Thorac Surg* 1998;65:331–5.
14. Reyes L, Parvez Z, Nemoto T, Regal AM, Takita H. Adrenalectomy for adrenal metastasis from lung carcinoma. *J Surg Oncol* 1990;44:32–4.
15. Raviv G, Klein E, Yellin A, Schneebaum S, Ben-Ari G. Surgical treatment of solitary adrenal metastases from lung carcinoma. *J Surg Oncol* 1990;43:123–4.
16. Kirsch AJ, Oz MC, Stoopler M, Ginsburg M, Steinglass K. Operative management of adrenal metastases from lung carcinoma. *Urology* 1993;42:716–9.
17. Ayabe H, Tsuji H, Hara S, Tagawa Y, Kawahara K, Tomita M. Surgical management of adrenal metastasis from bronchogenic carcinoma. *J Surg Oncol* 1995;58:149–54.
18. Kim SH, Brennan MF, Russo P, Burt ME, Coit DG. The role of surgery in the treatment of clinically isolated adrenal metastasis. *Cancer* 1998;82:389–94.
19. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Eng J Med* 2004;350:351–60.
20. American Society of Clinical Oncology. Treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–53.