

Adrenalectomy for Isolated Metastasis in Five Patients with Lung Cancer: Single Centre Experience and Review of the Literature

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ABSTRACT

Isolated adrenal metastasis from non-small cell lung cancer (NSCLC) is a rare event. Nonsurgical treatment of a solitary adrenal metastasis is associated with poor survival. However, in the aspect of long-term survival, the role of adrenalectomy for isolated metastasis is unclear. Here, we reported our experience with surgical treatment of solitary adrenal metastasis in patients with NSCLC whose primary tumor control were achieved and reviewed current literature. Between the 2001 and 2009, five patients underwent curative adrenalectomy (in 1 patient it was bilateral) for suspected solitary adrenal metastasis after surgical treatment of NSCLC. The pathological examination confirmed in 3 cases a NSCLC metastasis while in 2 cases it was a benign lesion. In the follow-up period, all of the 3 patients with adrenal metastasis had recurrence of NSCLC. Recurrence was local (in the operated adrenal bed) in 2 patients. Palliative radiotherapy focalized to adrenal bed was given to one of the patient with local recurrence. This patient is currently alive 51 months after the adrenalectomy. The other patient with local recurrence died 24 months after the adrenalectomy. Recurrence was systemic (brain and contralateral adrenal gland) in 1 patient who was treated with contralateral adrenalectomy and surgical resection of the cranial metastasis followed by cranial radiotherapy. The patient who underwent bilateral adrenalectomy for metastatic lung cancer died of wide-spread metastatic disease, 79 months after the adrenalectomy. In conclusion, survival benefit can be obtained after complete resection of isolated adrenal metastasis in patients with NSCLC. Therefore, resection of isolated adrenal metastasis should be considered if the primary NSCLC is resectable.

Keywords: Adrenalectomy, Lung cancer, Solitary adrenal metastasis

ÖZET

İzole Sürenal Metastazlı Beş Akciğer Kanseri Olgusunda Adrenalektomi: Tek Merkez Deneyimi ve Literatürün Gözden Geçirilmesi

Küçük hücreli dışı akciğer kanserinin (KHDAK) izole adrenal metastazı nadir görülür. Soliter adrenal metastazın cerrahi dışı tedavi yöntemlerinde sağkalım kısadır. Bununla beraber, uzun sağkalım açısından, izole adrenal metastazda adrenalektominin rolü net değildir. Burada, primer tümör kontrolü sağlanmış ve soliter adrenal metastazı cerrahi ile tedavi edilmiş KHDAK hastalarındaki deneyimimiz sunuldu ve güncel literatür derlemesi yapıldı. Soliter adrenal metastazı şüphesiyle, 2001-2009 yılları arasında beş hastaya, KHDAK cerrahi tedavisi sonrası küratif adrenalektomi (bir hastada bilateral adrenalektomi) operasyonu yapıldı. Patolojik inceleme sonucunda, 3 olguda KHDAK metastazı saptanırken, 2 olguda benign lezyon saptandı. İzlemede, adrenalektomiyle adrenal metastazı kanıtlanmış 3 hastanın hepsinde KHDAK rekürrensi oldu. Rekürrens, 2 hastada lokal (opere edilmiş adrenal yatak) idi. Lokal rekürrenseli hastaların birine adrenal yatağa yönelik palyatif radyoterapi verildi. Bu hasta adrenalektomiden 51 ay sonrasında olmak üzere hala hayattadır. Lokal rekürrenseli diğer hasta, adrenalektomiden 24 ay sonrasında ex oldu. Rekürrens 1 hastada sistemikti (beyin ve kontralateral adrenal bez), bu hasta kontralateral adrenalektomi ve beyin metastazına yönelik cerrahi rezeksiyon ardından kraniyal radyoterapi ile tedavi edildi. Metastatik akciğer kanseri nedeniyle bilateral adrenalektomi operasyonu yapılan hasta, adrenalektomiden 79 ay sonrasında yaygın hastalık ile ex oldu. Sonuç olarak, KHDAK hastalarında izole adrenal metastazın tam cerrahi rezeksiyonu ile sağkalım avantajı elde edilebilir. Bu nedenle, primer KHDAK rezektabl ise, izole adrenal metastazın rezeksiyonu dikkate alınmalıdır.

Anahtar Kelimeler: Adrenalektomi, Akciğer kanseri, Soliter adrenal metastaz

INTRODUCTION

The adrenal gland is a frequent site for metastasis from lung carcinoma. In patients with non-small cell carcinoma (NSCLC), the occurrence of adrenal metastasis is usually accompanied by metastasis in other organs.¹ The incidence of solitary adrenal metastasis from NSCLC is low, it was evaluated in 2 prospective studies to be only 1.6%, and 3.5%.^{1,2} Surgical treatment for metastatic lesions from lung cancer is seldom performed. The detection of adrenal metastasis usually is indicative of advanced disease stage at which a nonoperative treatment usually is used.² Because of the low incidence of isolated adrenal metastasis, there is limited understanding of the efficacy of adrenal resection.³ Several long-term survivors after surgical resection for a solitary adrenal metastasis from NSCLC have been reported in case reports and case series with a small number of patients.^{2,4-29} Herein, we report five patients of NSCLC with a suspected solitary adrenal metastasis treated surgically. The pathologic examination confirmed in 3 cases a NSCLC metastasis. In contrast to the expected short survival in lung cancer with distant metastasis, they achieved prolonged survival after combined treatment regimens. These cases were presented and current literature was reviewed.

PATIENTS AND METHODS

Between the 2001 and 2009, five patients of 48-71 years of age with operated NSCLC were found to ha-

ve an isolated adrenal mass. In two patients (Patients No.1 and 2), the presentation of solitary adrenal masses was synchronous, in remaining three patients, the presentation of adrenal masses was metachronous. After an extensive workup to exclude metastasis to other sites, all adrenal masses that were compatible with an isolated adrenal metastasis were completely resected. We did not perform any fine needle aspiration of adrenal masses. In all patients who were accepted for curative adrenalectomy, the primary NSCLC had been treated by complete surgical resection and systematic nodal dissection. In one patient (Patient No.4), mediastinoscopy was performed prior to lung resection. Only one patient (Patient No.2) had systematically received preoperative platinum-based chemotherapy, three patients received postoperative platinum-based chemotherapy. The remaining patient (Patient No.5) did not receive adjuvant chemotherapy. Radiation therapy of the mediastinum was given to two patients (Patient No.4 and 5). Patient No.3 received adjuvant radiotherapy focalized on primary tumor bed.

In all patients, subcostal transverse laparotomy was chosen for adrenal surgery and a wide surgical exposure was obtained. The macroscopic adjacent organ invasion was not observed in any of patients. Metastatic adrenal gland was resected carefully with surrounding tissue and care was taken to avoid capsular injury. Curative resection rendering the patient free of disease was possible and surgical margins were negative in all patients. However, tumor invaded the

adrenal capsule in 2 patients. All patients presenting with local recurrences had capsular invasion of the adrenal gland on histologic examination. There were no perioperative deaths or postoperative complications. Prior or after adrenalectomy, no particular criteria were defined to give any neoadjuvant/adjuvant treatment including radiotherapy focalized on adrenal bed, or platinum-based chemotherapy protocols. Decisions for complementary treatment were made on a case-by-case basis. We defined a disease-free interval (DFI) corresponding to the time interval between the surgical treatment of the primary tumor and the diagnosis of the adrenal metastasis. In patients with synchronous adrenal masses, the DFI was defined as zero. For a patient with multiple episodes of adrenalectomy, DFI was calculated from the diagnosis date of the first adrenal metastasis. Disease-free survival (DFS) was defined as the time interval from the adrenalectomy to the date of disease recurrence. Survival was calculated from the date of adrenalectomy to death or the date of last follow-up. All the patients underwent a strict follow-up every 3 months. Survival curve of the reported lung cancer patients who underwent adrenalectomy for solitary adrenal metastasis was estimated by the Kaplan-Meier method.

RESULTS

The characteristics and clinical outcomes of these patients are outlined in Table 1.

In patient No.1, the imaging techniques [computed tomography (CT) and magnetic resonance imaging (MRI)] could not be sufficient to determine whether the lesion represents a metastasis or an adenoma. He underwent left adrenalectomy for suspected synchronous solitary adrenal metastasis from NSCLC. But the histologic findings confirmed the diagnosis of adrenocortical hyperplasia. Patient No.2, underwent integrated positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (¹⁸F-FDG)-CT (PET-CT). Pathologic ¹⁸F-FDG uptake was found in the primary tumor localized at right upper lobe of the lung, mediastinal lymph nodes and left adrenal mass. Clinical staging showed stage IV (T2N2M1) disease. She received six cycles of combination neoadjuvant chemotherapy consisting of cisplatin 75 mg/m² and docetaxel 75 mg/m², on day 1, every 21 days. A prominent metabolic response in primary tumor was ob-

tained on the PET-CT evaluation after 6 cycles of chemotherapy. The findings in the left adrenal gland were constant and compatible with an adrenal metastasis. Another 3 cycles of the same chemotherapy regimen and 3 cycles of single agent docetaxel regimen were administered to the patient. Metabolic response of the primary tumor was stable but an increased FDG uptake in left adrenal gland was obtained when comparing with the prior PET-CT evaluation. After then, she underwent lung resection and left adrenal gland resection. Interestingly, pathological examination revealed an adenoma of the adrenal gland. Patient No.3, with recurrence in adrenal bed refused the re-operation. Because of the poor performance status (ECOG 3), radiotherapy and chemotherapy were not considered and best supportive care was administered to the patient and he died 12 months after the recurrence. In Patient No.4, an unresectable local recurrence was detected during the intraoperative evaluation and he was treated with palliative radiotherapy (total dose; 45 Grays) focalized on the adrenal bed. This patient is currently alive 44 months after the recurrence. In patient No.5, 18 months after left adrenalectomy, a solitary brain metastasis was detected and surgical resection of the metastasis was performed followed by cranial radiotherapy. Two years after left adrenalectomy, a solid mass of 4 cm was visualized in the right adrenal gland by CT scan. Following 2 cycles of chemotherapy consisting of carboplatin and gemcitabine, right adrenalectomy was performed and the histopathological study showed metastatic adenocarcinoma. Gefitinib (Iressa®) 250 mg tablet was administered to the patient orally once a day for 16 months until the progression. Because of the contralateral lung metastasis and supraclavicular lymph nodes metastases, she received 5 cycles of chemotherapy consisting of docetaxel 75 mg/m², on day 1, every 21 days. Because of the progression, another 7 cycles of chemotherapy with vinorelbine 25 mg/m², on days 1 and 8, every 21 days, were administered to the patient. She died of wide-spread metastatic disease in 2009, 8 years after initial presentation.

DISCUSSION

The incidence of adrenal mass in patients with operable NSCLC was reported to range from 4% to 18%, approximately 60% of these were benign.¹ Concer-

Table 1. Characteristics of patients who underwent adrenal gland resection for isolated metastasis from NSCLC

Characteristics of patients	Patient Number 1	Patient Number 2	Patient Number 3	Patient Number 4	Patient Number 5*
Gender	Male	Female	Male	Male	Female
Age (years)	65	48	71	53	56
Histologic type of primary lung cancer	Squamous	Squamous	Large cell neuroendocrine	Adenocarcinoma	Adenocarcinoma
Stage of primary lung cancer	pT2N0	pT1N0	pT2N0	pT1N2	pT2N1
Pulmonary resection	Lobectomy and MLND	Lobectomy and MLND	Lobectomy and MLND	Lobectomy and MLND	Pneumonectomy and MLND
Therapy for lung cancer	Four cycles of adjuvant chemotherapy	Twelve cycles of neoadjuvant chemotherapy	Adjuvant radiotherapy and six cycles of adjuvant chemotherapy	Adjuvant radiotherapy and four cycles of adjuvant chemotherapy	Adjuvant radiotherapy
Adrenal gland masses	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Contralateral and later ipsilateral
Adrenal masses location	Left	Left	Left	Left	Left and later right
Size of adrenal masses (cm)	4x2	1.4x1.4	4X3	6.5X6	8X6.5 (left) and 4X4 (right)
Diagnostic tool for detection of adrenal masses	CT, MRI	CT, PET-CT	CT, PET-CT	CT	CT
Pathology of adrenal masses	Adrenocortical hyperplasia	Adenoma	Metastasis	Metastasis	Metastasis
Therapy for adrenal metastasis	-	-	Six cycles of neoadjuvant and four cycles of adjuvant chemotherapy	Neoadjuvant six cycles of chemotherapy	Neoadjuvant chemotherapy and adjuvant Gefitinib for contralateral adrenal gland metastasis
DFI after lung resection (months)	0	0	10	12	15
DFS after adrenalectomy (months)	36	16	12	7	18
Survival after adrenalectomy (months)	36	16	24	51	79
Location of recurrence / distant metastases	-	-	Left adrenal bed	Left adrenal bed	Brain and contra-lateral adrenal gland
Status	Alive	Alive	Dead	Alive	Dead

Abbreviations: MLND, mediastinal lymph nodes dissection; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography; DFI, disease free interval; DFS, disease free survival; * Patient who underwent bilateral adrenalectomy

ning the therapeutic management of a solitary adrenal mass from operable NSCLC, the first step is to determine whether it represents a metastasis or an adenoma.³⁰ With improved imaging and recent techniques, such as contrast medium washout measurement on CT and chemical-shift MRI, only a small proportion of adrenal masses cannot be characterized accurately.^{31,32} The small numbers of masses that remain indeterminate after these investigations, require PET imaging or percutaneous biopsy. In many places the lack of availability of PET presently limits its clinical use.³¹ Metastatic disease involving the adrenal gland has been suggested when these adrenal lesions show changes on serial CT scans. Unfortunately, the determination of benignity or malignancy of adrenal masses by serial CT scans over several months in a cancer patient adds unnecessary delay in the institution of definitive treatment.^{1,30} Therefore, the presence of unilateral adrenal mass in patients with otherwise operable NSCLC should not preclude thoracotomy without pathologic proof of metastatic disease.¹ Similarly, in a patient of our series (Patient No.1), CT and MRI could not be sufficient to determine whether the lesion in adrenal gland represents a metastasis or an adenoma. PET imaging was not available at that time in our city. The patient eventually underwent surgical resection of the primary tumor followed by adrenalectomy. Fine needle aspiration biopsy (FNAB) under radiological guidance is regarded as a useful tool in resolving these diagnostic problems.³³⁻³⁵ It is a relatively safe and effective means of achieving a definitive diagnosis in doubtful cases, however, this procedure may be nondiagnostic or complicated due to anatomic constraints.^{14,36-40} It has been reported that samples could be taken insufficiently, thus resulting in nondiagnostic specimens as frequently as 28%.³⁷ When insufficient material results from a biopsy, repeat aspiration or even the performance of an adrenalectomy should be considered.^{14,36,39} Because of sampling error, there is always a possibility that percutaneous biopsy could yield false-negative diagnoses of malignancy. Therefore, even if the biopsy reveals negative test results, there is still no guarantee that the adrenal gland is free from malignancy.^{14,37,39} Because of the similarity of the cytologic appearance between normal adrenal cortex and adrenal adenoma, it is essential that the needle be placed correctly in the mass during FNAB to obtain a high degree of accuracy.³⁰ Welch and coworkers, re-

viewing 277 percutaneous adrenal biopsies, reported an overall accuracy of 90%. The positive predictive value for metastasis was 99%, however, the negative predictive value was approximately 80%.³⁸ In patient No.1, left adrenalectomy was performed without histologic confirmation for suspected adrenal metastasis. The size of adrenal mass of this patient was 4 x 2 cm. Many studies have suggested that the size of unilateral adrenal mass as seen on a CT scan is an important criterion for differentiating adenomas from metastases.^{30,36} Lesions that are >3 cm in size are more likely to signify metastases, but benign disease is still possible^{30,36}, as in our patient No. 1. It was reported that, at least for tumors larger than 3.5 cm, biopsy could be avoided and surgical intervention directly performed, regardless of their cytologic appearance by FNAB.^{14,30} Besides, in cases of metachronous metastasis, when imaging examinations performed during follow-up clearly demonstrate the recent occurrence of an adrenal mass, adrenalectomy can be performed without histologic confirmation of the metastasis.² Accordingly, we considered a recent occurrence of adrenal mass during follow-up of our three patients (Patients No.3,4,5) as highly suspected for malignancy so the invasive diagnostic procedures were not needed.

Whole-body FDG PET imaging has proved encouraging in differentiating benign from metastatic adrenal mass in patients with malignancies.^{41,42} It has a better sensitivity, specificity, and accuracy in identifying an adrenal metastasis than MRI or CT scan, with accuracy ranging between 92% and 100%.^{43,44} But, there are still considerable false-positive and false-negative results on imaging studies. The commonly reported causes of false-positive results have been due to pheochromocytomas and benign adenomas.^{45,46} Sung et al. also reported three cases of false-positive PET/CT in patients with lung cancer.⁴⁷ Kim HK et al. suggest that when adrenal mass is considered benign on CT or PET/CT, surgical resection of NSCLC is indicated, when adrenal mass is indeterminate on CT or PET-CT, histopathological confirmation is needed to determine the nature of adrenal mass.⁴⁸ In a most recent review, the authors states that a PET-positive adrenal lesion, however, should still undergo biopsy to confirm metastatic disease if this is the sole site of metastasis.⁴⁹ In consistent with this opinion, in one of the our patients (Patient No.2), despite an adrenal mass compatible with metastasis

on preoperative CT and PET scanning, it was found to have a benign adenoma on postoperative histology. If we had decided not to perform surgical resection of NSCLC in this patient due to malignant findings of imaging studies, she would have lost the opportunity of curative resection even though adrenal mass was benign.

Resection of isolated adrenal metastasis should be considered if the primary NSCLC is resectable.^{11,15,17} Published results of non-surgical therapy demonstrated median survival periods less than 6 and 8.5 months, respectively.^{8,11} There is evidence to believe that adrenalectomy offers good therapeutic results when control of the primary lesion is achieved, and in cases with severe symptoms caused by the adrenal metastasis.⁶ In 1982, Twomey et al. documented prolonged survival after adrenalectomy, along with curative management of the primary cancer in the lung, for patients with clinically isolated adrenal metastasis.⁴ Since then, several similar reports have confirmed the feasibility of this approach. A summary of these case studies (Table 2) demonstrates that selected lung cancer patients with an isolated adrenal metastasis can undergo resection with a reasonable long-term survival.^{2,4,29} The median survival of the reported patients calculated with the Kaplan-Meier method was 24 months and the 1-, 2-, 3-, 5-year survival rates were 71.7%, 48.4%, 38.4%, 33.5%, respectively (Figure 1). Luketich and Burt described 14 patients with NSCLC and adrenal metastases, eight of whom were treated with surgical excision and chemotherapy and the other six with chemotherapy alone.¹¹ The median survival in the surgical group was significantly greater than that in the chemotherapy group (31 versus 8.5 months; $p = 0.03$). The largest series has been published by Porte et al.⁷ Their study included 43 patients between 1987 and 1998 from eight centers. Overall median survival was 11 months, with three patients surviving more than 5 years. It has been stated that surgical treatment of solitary adrenal metastasis from resectable NSCLC could potentially improve survival.¹⁷ Sarella et al. and Strong et al. reported their laparoscopic adrenalectomy (LA) experience in cancer patients with isolated adrenal gland metastasis from the same center.^{28,50} There were no significant differences in survival when comparing the LA versus open adrenalectomy for NSCLC patients.^{28,50} The median survival of 39 lung cancer patients included in their study was 17

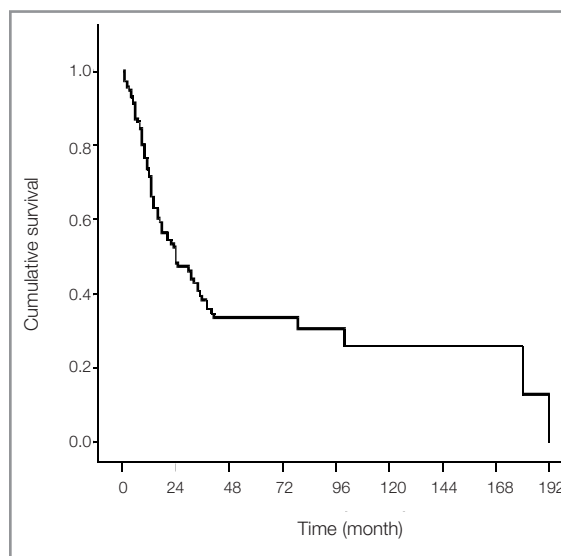


Figure 1. Survival of the reported patients ($n = 118$) after resection of solitary adrenal metastasis from resected NSCLC calculated with the Kaplan-Meier method.

(The patients reported by Lo¹⁰, Luketich¹¹, Kim¹⁵, Porte¹⁷, Heniford¹⁸, Itou²⁶, and Strong²⁸ were not included in Kaplan-Meier analysis because of the lack of the data on individual survival. Only summarized data are available for these patients).

months.²⁸ It was concluded that LA for metastatic adrenal lesions is safe, with equivalent long-term oncological outcomes providing the additional benefits of a minimally invasive technique.^{28,29,50} A review compiling reports of 11 articles with 60 patients after resection of adrenal metastases from lung cancer showed a median survival between 14-24 months.⁵¹ The survival of our series is acceptable, demonstrating that surgical treatment of adrenal metastasis in patients with NSCLC has to be considered. Recently, a summary of patients with metachronous disease were reported by Abdel-Raheem et al.²⁷ Overall median survival for patients with adrenalectomy and chemotherapy ($n = 8$) was 19 months and with adrenalectomy alone ($n = 5$) 14 months. Therefore, after adrenalectomy, systemic chemotherapy should also be given for possible micrometastatic disease.^{27,51}

The rate of local recurrence in 94 patients who underwent adrenalectomy for isolated adrenal metastasis was 17%.²⁸ Of the 94 patients, 39 had NSCLC histology and there were no significant differences in the rate of local recurrence when comparing the NSCLC histology versus all other histologies.²⁸ In a

Table 2. Survival of the reported patients who underwent surgical treatment of primary non-small cell lung cancer and solitary adrenal gland metastasis

First Author [Reference]	Year of Publication	Number of Patients	Survival Times After Adrenalectomy (months)	Median Survival After Adrenalectomy (months)
Porte HL ²	1998	11	4,4,6,8,13,24,66+,10+,6,14,6+	6
Twomey ⁴	1982	2	180,192	
Raviv ⁵	1990	3	35,25,24	
Reyes ⁶	1990	4	36+,48+,13,10	
Kirsch ⁷	1993	1	24+	
Higashiyama ⁸	1994	5	40+,24+,17,20,9	
Ayabe ⁹	1995	3	108+,72+,20	
Lo ¹⁰	1996	10	NA	13
Luketich ¹¹	1996	8	NA	31
Urschel ¹²	1997	1	108+	
Wade ¹³	1998	14	0.7,0.9,3,5,6,11,11,13,23+,25+,32,34,36,61+	18
Bandinelli ¹⁴	1998	4	18,9,10+,8+	
Kim ¹⁵	1998	17	NA	14
de Perrot ¹⁶	1999	1	60+	
Porte HL ¹⁷	2001	43	NA	11
Heniford ¹⁸	1999	2	NA	
Bretcha-Boix ¹⁹	2000	5	38,52+,58+,16+,8+	
Ambrogj ²⁰	2001	5	66+,116+,90+,30,18	
Hasan ²¹	2002	1	13	
Mercier ²²	2005	23	7,41,100,16,110+,94+,6,11,2,16,5,2,9,30+,8,34,41+,16,10,13,14+,9+,0.3+	13.3
Pfanschmidt ²³	2005	11	72+,10,6,13,9+,10,12,31,40,31,9	12.6
Lucchi ²⁴	2005	10	18,9,14,80+,14,12,43+,38,44+,37+	18
Muñoz ²⁵	2006	1	48+	
Ito ²⁶	2006	6	NA	24
Abdel-Raheem ²⁷	2002	1	10+	
Strong ²⁸	2007	39	NA	17
Sebag ²⁹	2006	9	68+,66+,24,24+,23,22,19+,1,1+	23
Unek	-	3	24,51+,79	

Abbreviations: NA: not available; +: indicates patients still alive at given number of months.

Table 3. Summary of the 8 patients reported in the literature who underwent bilateral adrenal gland resection for isolated metastasis from NSCLC

First Author [Reference]	Year of Publication	Number of Patients	Primary Lung Cancer Histologic Type	Adrenal Gland Metastasis Features	Adrenalectomy	Survival After Adrenalectomy (months)	Status
Reyes ⁶	1990	1	Large cell carcinoma	Synchronous with lung cancer	Both adrenal glands at the same operation	36	Alive
Urschel ¹²	1997	1	Large cell carcinoma	Metachronous with lung cancer	Both adrenal glands at the same operation	108	Alive
Heniford ¹⁸	1999	1	NA	NA	Both adrenal glands at the same operation	NA	NA
Bretcha-Boix ¹⁹	2000	1	Adenocarcinoma	Metachronous with lung cancer	First Right, 15 months later, Left	38	Dead
Bretcha-Boix ¹⁹	2000	1	Large cell carcinoma	Synchronous with lung cancer	Both adrenal glands at the same operation	8	Alive
Hasan ²¹	2002	1	NA	NA	Both adrenal glands at the same operation	13	Dead
Lucchi ²⁴	2005	1	Large cell carcinoma	Metachronous with lung cancer	First Left, 14 months later, Right	44	Alive
Muñoz ²⁵	2006	1	Adenocarcinoma	Metachronous with lung cancer	Both adrenal glands at the same operation	48	Alive
Current case with bilateral adrenalectomy (Patient No.5)	-	1	Adenocarcinoma	Metachronous with lung cancer	First Left, 24 months later, Right	79	Dead

Abbreviations: NA, not available

study by Porte et al, seven patients out of 43 NSCLC patients who underwent adrenalectomy, had developed recurrence in the adrenal bed regardless of the surgical approach used.¹⁷ The authors stated that the recurrences in adrenal bed argues in favor of systematic adjuvant radiotherapy delivered to the adrenal bed. Our three patients with metastatic carcinoma did not receive radiotherapy to the adrenal bed after adrenalectomy. The surgical margins of all the three patients were negative but local recurrences have developed in two patients with capsular invasion (Patients No.3, 4). However, local recurrence has not developed in the other patient (Patient No.5) without capsular invasion. When our results are taken into account, radiotherapy to the adrenal bed after adrenalectomy may be a reasonable option to prevent the local recurrences in patients with capsular invasion although surgical margins are negative. Randomized prospective trials are needed to evaluate the role of adjuvant radiotherapy to the adrenal bed after adrenalectomy in patients with NSCLC. The rarity of solitary adrenal metastasis makes a randomized prospective trial comparing different treatment regimens unlikely. Surgical resection seems the best option for a potential cure, or at least the best palliative therapy compared to nonsurgical treatments. Accordingly, few reports have been published on the role of radiotherapy on adrenal metastasis.⁵²⁻⁵⁴ Soffen and colleagues reported the results of palliative radiotherapy in 9 patients with lung carcinoma and isolated adrenal metastasis, whose median survival was 6 months.⁵² Only Miyaji and co-workers reported a case of long-term survival exceeding 34 months after radiotherapy for a metachronous adrenal metastasis, in a patient who underwent resection of the primary NSCLC.⁵⁴

One of the our patients operated on for solitary left adrenal metastasis, developed a right adrenal metastasis and was operated on again. The time interval between these adrenalectomy operations was 2 years. In English medical literature, only 8 cases of bilateral adrenalectomy for metastatic lung cancer were reported.^{6,12,18,19,21,24,25} Table 3, summarizes the data from the literature regarding patients who have undergone potentially curative lung resection and bilateral adrenal resection. In two of the patients, presentation of bilateral adrenal metastases were synchronous with lung cancer^{6,19}, in remaining six patients, bilateral adrenal metastases presented metachronously with lung cancer.^{12,18,19,21,24,25} Six of the 8 cases underwent both

right and left adrenalectomy at the same operation.^{6,12,18,19,21,25} One patient underwent left adrenalectomy for a solitary adrenal gland metastasis and 14 months later, contralateral adrenalectomy for a new solitary metastasis.²⁴ The other patient developed recurrent metastases in both adrenals 15 months after right adrenalectomy.¹⁹ Therefore, he underwent left adrenalectomy and resection of the recurrent lesion in right adrenal bed. Eight months later, the patient were treated by radiosurgery for three metastases in the brain.¹⁹ Similarly, our patient underwent left adrenalectomy and 2 years later right adrenalectomy. During the time interval between the left and right adrenalectomy operations, she underwent surgical resection of the solitary brain metastasis followed by cranial radiotherapy. As far as we know, a patient with bilateral adrenal metastases who underwent bilateral adrenalectomy and surgical resection of the solitary brain metastasis from lung cancer has not been previously reported. The presence of resected, isolated brain metastasis does not appear to be a contraindication for adrenalectomy.³

Some authors suggest that the most appropriate patients for the resection of adrenal gland metastasis are the patients whose disease progresses slowly after lung resection.^{7,8} Accordingly, in some case series, it was found that DFI of less than 6 months and synchronous metastasis were associated with worse survivals.^{3,8,15,22,23} In contrast to these studies, it was reported that adrenalectomy for synchronous versus metachronous lesions showed no difference in survival.^{17,28,29}

In conclusion, survival benefit can be obtained after complete resection of isolated adrenal metastasis in patients with NSCLC. Therefore, resection of isolated adrenal metastasis should be considered if the primary NSCLC is resectable. On the other hand, during preoperative evaluations, the difficulties in differentiating coincidental benign adrenal masses from synchronous metastatic adrenal lesions in patients with lung cancer still continue.

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