Check for updates

Clinical Characteristics, Molecular Phenotyping, and Management of Isolated Adrenal Metastases From Lung Cancer

Antonio Mazzella,[1] Mauro Loi,[2] Audrey Mansuet-Lupo,[3] Antonio Bobbio,[1] Helene Blons,[4] Diane Damotte,[3] Marco Alifano[1]

Abstract

Adrenal involvement is frequent in metastatic non–small-lung cancer. Patients with oligometastatic (≤ 3 metastases) disease treated with adrenalectomy have a 5-year overall survival of 34.5%. Next generation sequencing identified mutational discordance between primary tumors and metastases in 20% of cases, thus offering insights into tailored treatment in the setting of oligometastatic lung cancer.

Introduction: Adrenal gland metastases occur in up to 20% of patients with non–small-lung cancer. In selected cases with limited burden of disease, surgery may be offered to improve patient outcome; furthermore, tissue analysis would provide useful information on genotype of primary and secondary neoplasms. **Materials and Methods:** We report our experience in the management of adrenal metastasis by retrospectively reviewing data of 21 consecutive patients treated with curative intent to the primary tumor followed by adrenalectomy in a 15-year time span. Targeted next generation sequencing was performed to compare molecular profile of primary lung cancers and adrenal metastases. Patient overall survival was assessed by Kaplan-Meier method, using adrenalectomy as time zero. Survival rates were compared by log rank test. **Results:** No surgery-related mortality or morbidity was observed. Median survival was 50 months; 5-year overall survival was 34.5% (95% confidence interval, 12%-66%). No significant survival difference was observed with respect to timing of onset (synchronous vs. metachronous) or side (homolateral vs. contralateral) of adrenal metastasis, T or N status of primary lung cancer, mutational asset, and histologic type. Mutations in *TP53* genes were found in 61% and 85% of primary and metastatic tumors, respectively. In 3 of 15 cases, we found differences between molecular mutation patterns in primary lung cancer and corresponding adrenal metastasis. **Conclusions:** Adrenalectomy is a safe and effective approach in selected cases. Discordance between primary and secondary tumor mutational profile was found in 20% of assessable patients.

Clinical Lung Cancer, Vol. 20, No. 6, 405-11 © 2019 Elsevier Inc. All rights reserved.
Keywords: Ablative therapy, NSCLC, Oligo-metastatic disease, Radiotherapy, Surgery

A.M. and M.L. contributed equally to this article as first authors.

[1]Thoracic Surgery Department, Paris Center University Hospital, Assistance Publique — Hôpitaux de Paris, Paris Descartes University, Paris, France
[2]Radiotherapy Department, Hopital Tenon, AP-HP, Paris, France
[3]Pathology Department, Paris Center University Hospital
[4]Pharmacogenetics and Molecular Oncology Unit, Paris Center University Hospital, Assistance Publique — Hôpitaux de Paris, Paris Descartes University, Paris, France

Address for correspondence: Marco Alifano, MD, PhD, Service de Chirurgie Thoracique, Hôpitaux Universitaires Paris Centre, 27 Rue du Faubourg Saint Jacques, 75014 Paris, France
E-mail contact: marco.alifano@aphp.fr

Introduction

Lung cancer ranks first and second in mortality worldwide among men and women, respectively.[1] At diagnosis, about one-half of patients with lung cancer have distant metastases.[2] The most common metastatic sites are brain, lung, adrenal glands, bone, and liver. On the basis of observation of improved long-term survival in patients with limited disease burden (generally up to 5 metastases) compared with patients with widespread dissemination, an intermediate state between localized and systemic disease ("oligometastatic" disease) has been proposed.[3,4]

Oligometastatic disease is found in about 30% of metastatic lung cancers[5-7]; the reported overall survival in this setting exceeds the generally expected 5-year survival of widespread metastatic disease

(30%[8,9] vs. 4% to 6%[10-12]), even in patients with metastatic disease at initial presentation.[13] This novel concept implies the possibility to treat isolated or limited metastatic sites with focal therapies such as surgery or radiotherapy.

Most interestingly, recent advances in genomics offer the opportunity to comprehensively study the disease genotype in both primary and secondary tumors, to highlight specific mutations of driver genes, thus allowing to test sensitivity to molecular target agents in case of polymetastatic relapse.[14]

Among potential sites of dissemination, isolated metastatic involvement of the adrenal gland is observed in up to 20% of patients with NSCLC.[6,15,16] Patients with isolated synchronous or metachronous adrenal metastases may be offered surgery as part of a multimodality treatment; however, few experiences, mainly represented by small surgical series, are available in the literature.[8,9,16-19] Little is known on prognostic factors: it has been suggested that patients with synchronous lesions would have a significantly worse prognosis than patients with metachronous metastases, whereas ipsilateral (with primary lung cancer) adrenal metastases would be associated with more favorable outcomes.[8,9] Similarly, scarce information is available in the literature about molecular patterns of metastasis as compared with primary lung neoplasm. To provide further insight into these topics, we aimed at reviewing our experience in the management of this subset of patients with lung cancer with oligometastatic disease.

Materials and Methods

We retrospectively reviewed clinical and pathologic files of all patients with lung cancer and synchronous or metachronous isolated adrenal metastases, treated by local treatments of both primary and metastasis in our center between 2001 and 2017. Data were obtained from clinical, surgical, and pathologic records. Metastases existing at diagnosis of primary cancer or within 6 months were considered as synchronous, and their treatment was performed before (at least 1 month) or after (at maximum 4 months) primary lung surgery.

The research was conducted according to recommendations outlined in the Helsinki declaration as well as to French laws on Biomedical Research. Institutional review board approval was obtained (CERC-SFCTCV-2017-5-28-12-24-25-AlMa). All patients or relatives (in case of deceased patients) gave their informed consent to participate and allowed the use of their data.

Indications for Loco-regional Treatments

In our institution, decisions of treatments of lung cancer are based on an individual based discussion during a weekly multidisciplinary meeting. The current policy of our team is to consider loco-regional treatments for oligometastatic disease only in case of a maximum number of metastatic lesions ≤ 3. Only adrenal and cerebral metastasis are considered to be amenable to local treatments as part of the management of oligometastatic lung cancer.

Patients are considered for loco-regional treatments if: (1) they are fit enough to tolerate the possible association of chemotherapy with double-site local treatments (including lung resection and/or adrenal resection): performance status should be ≤ 1 and nutritional status preserved; (2) the operative risk is considered low on the basis of respiratory reserve and cardiac assessment; (3) there is no clinical mediastinal nodal involvement; (4) T stage parameter is < 4; (5) the patient

has clearly expressed willingness to adhere to a heavy multidisciplinary treatment, including, when indicated, double-site surgery.

Loco-regional Treatments

Lobectomy or pneumonectomy with radical nodal dissection was carried out through standard thoracotomy in all the cases. In patients who were not eligible for primary tumor surgery, adrenalectomy was performed only if the lung tumor was controlled by chemoradiotherapy (complete response). Adrenal metastases resection was performed by the thoracic surgery team via laparoscopy or laparotomy, with no strict rules, but generally depending on dimensions of metastases and possible involvement of adjacent structures preventing a satisfactory dissection through laparoscopy. Phrenotomy through thoracotomy was an option for small synchronous homolateral lesions.

Collected Data

Patients' characteristics, treatment procedures, and short-term outcomes were collected using a standardized case report form. We recorded clinico-demographic and pathologic data (age, gender, smoking history, location of the tumor and the metastasis, timing of metastases, primary tumor diameter, tumor staging, nodal status) and treatment-related variables (use of adjuvant and neoadjuvant chemotherapy, type of surgery for primary tumor). Tumor stage was reattributed according to the 7th TNM edition.[10]

Molecular Analysis

Tumoral DNA was extracted from the formalin-fixed paraffin-embedded (FFPE) block containing the highest percentage of tumor cells, with macrodissection if necessary, in order to obtain at least 30% of tumor cells. DNA was extracted from FFPE samples using the Maxwell 16 FFPE Plus LEV DNA Purification Kit (Promega Corp., Madison, WI) and quantified using Qubit fluorometric quantitation device (Thermo Fisher Scientific, Waltham, MA). Next generation sequencing (NGS) analysis using the Colon and Lung Cancer Research Panel V2 (Life Technologies) was performed as previously described.[14] Gene amplification was defined by a coverage mean superior to 3SD.

Data Analysis, Follow-up, and Statistical Analysis

Data processing and analysis were performed with the statistical Software system SPSS (IBM SPSS Statistics, Version 21.0. Armonk, NY: IBM Corp. Released 2012). Correlation between variables was tested using the χ^2 test for categorical parameters and the t test or the Mann-Whitney test for, respectively, normally and not normally distributed parameters. Follow-up information was obtained by telephonic interview with patients, relatives (in case of deceased patients), and referring physicians. Municipality registers were checked to confirm information on vital status. Patient overall survival was assessed by the Kaplan-Meier method, using date of metastasectomy as time zero. The end of follow-up was September 30, 2017. Survival rates were compared by log-rank test. Significance was accepted at a level of $P < .05$.

Results

Demographic, clinical, and pathologic characteristics are presented in Table 1. Twenty-one adrenalectomies for adrenal

Table 1	Demographic, Clinical, and Pathologic Characteristics of Patients
Characteristic	**N (%)**
Gender	
Male	13 (65)
Female	7 (35)
Median age, y (range)	67 (52-80)
Primary lung cancer treatment	
Lung resection	18 (90)
Radio-chemotherapy	2 (10)
Surgical lung resection	
Lobectomy	14 (70)
Bi-lobectomy	2 (10)
Pneumonectomy	2 (10)
Histologic type	
Adenocarcinoma	14 (70)
Large-cell carcinoma	2 (10)
Squamous cell carcinoma	4 (20)
pT stage	
T1	4 (20)
T2	11 (55)
T3	3 (15)
T4	0 (0)
Tx (no intervention)	2 (10)
pN stage	
N0	8 (40)
N1	5 (25)
N2	5 (25)
Nx (no intervention)	2 (10)

metastasis were performed in our department in the study period; 1 patient was excluded from analysis owing to the removal of a non-metastatic incidental adrenal lesion (pheochromocytoma). In the remaining 20 patients, we observed 10 patients with metachronous and 10 patients with synchronous metastatic disease. In 1 patient with synchronous oligometastatic disease, there was an adrenal metastasis accompanied by a concurrent single cerebral metastasis; this last one was treated by surgery and adjuvant stereotactic radiotherapy on the residual cavity. In 18 patients, primary tumor was treated by surgery (14 lobectomies, 2 bi-lobectomies, 2 pneumonectomies); 2 patients were treated by conventional thoracic chemo-radiotherapy. Adrenalectomy was performed by laparoscopy, laparotomy, and phrenotomy through thoracotomy in 10, 9, and 1 cases, respectively.

Focusing on molecular assessment of primary cancer and adrenal metastasis, we found gene mutations on the primary and secondary tumor in 13 and 17 patients of 16 and 18 samples available for DNA analysis, respectively (Table 2). All wild-type tumors (n = 3) were squamous cell carcinomas. Among 14 patients in whom molecular analysis was available for both primary tumor and metastasis, we found the same mutational pattern in primary cancer and metastasis in 12 cases, whereas additional (n = 2) or missing (n = 1) mutations in the metastasis were detected in 3 patients. No clinical

or treatment-related variable was correlated with discordant mutational pattern in this subset of patients.

Results of histologic and molecular phenotype are summarized in Table 2. Mutations occurred principally in the *TP53* gene, in 11 lung primaries and 13 adrenal metastases, respectively; in most cases, they consisted of point mutation, without hotspot mutation. Driver genes, such as *EGFR* and *KRAS,* mutations were found in 2 and 3 primary tumors, respectively, and in 2 and 4 metastases, respectively. Interestingly, one patient exhibited an *EGFR* amplification only in the metastasis but not in the primary tumor, suggesting that amplification could be acquired during tumor progression. Likewise, a not-activating *BRAF* mutation occurred de novo in 1 metastasis. Other driver mutations were observed on the MAPK and PTEN pathways (Table 2).

Operative mortality and morbidity (both 1-month and 3-month) were zero. Median survival was 50 months, and 5-year overall survival was 34.5% (95% confidence interval, 12.5%-66.9%) (Figure 1).

No significant difference in overall survival were observed with respect to metachronous or synchronous presentation of metastatic disease, to ipsilateral or contralateral character of adrenal metastasis with respect to primary lung cancer, to T or N parameter of primary tumor, to histologic type, or to divergent mutational status between primary and metastatic tumor (Table 3).

Discussion

Prognosis of lung cancer associated with adrenal metastasis is generally poor. When metastatic disease is limited to adrenal gland, surgical resection of adrenal metastasis may be proposed and would lengthen survival.[18] Adrenalectomy (via laparoscopy or laparotomy) represents the gold standard in the "local" treatment of isolated adrenal gland metastases if the operation is technically possible and if patients are fit enough. Other therapeutic options include stereotactic body radiotherapy and radiofrequency ablation.[9] The benefit of surgical resection of isolated adrenal metastasis has been poorly evaluated: 2 pooled analyses of 13 and 10 series of resected adrenal metastasis, including a total of 98 and 114 patients, respectively, are available in the literature.[8,9] To our knowledge, molecular phenotyping of both primary and metastatic disease at adrenal level has not been reported so far. Thus, we aimed at performing NGS in lung and adrenal specimens, in the idea that this would provide additional information potentially useful in further management.

In our series, 3 patients had different mutations in the 2 tissues. One of them —with an additional mutation in metastasis- had a metachronous disease and received adjuvant chemotherapy after lung resection; in the 2 other cases, metastases were synchronous, and chemotherapy was administrated at the same time before lung and metastasis resection. The real mechanism of these additional molecular mutations in metastasis is unknown, but in the case of metachronous disease, we can advocate a possible genetic alteration linked to a drug-induced resistance after chemotherapy. In the other cases, where the additional mutation was present in the primary tumor and not in metastasis, this could be owing to tumor heterogeneity.

In recent years, some authors investigated molecular mutations on lung cancer tissue and on circulating plasmatic or cerebrospinal

Table 2	Molecular Alterations in Primary Lung Neoplasm Tissue and Adrenal Metastasis								
				Primary Lung Neoplasm Profile			**Metastasis Profile**		
Patient	Timing	Histology	Treatment Sequence	1st Mutation	2nd Mutation	PD-L1 (TPS, %)	1st Mutation	2nd Mutation	Additional Mutations	PD-L1 (TPS, %)
1	Meta	AC	LS-*pCT-AS	TP53 p.Gly245Val	—	1	TP53 p.Gly245Val	—	—	70
2	Sync	AC	nCT-LS-AS-aCT	KRAS p.Gly12Cys	**TP53 p.Gly199Val**	5	KRAS p.Gly12Cys	—	—	30
3	Meta	AC	LS.*AS	EGFR p.Gly719Ala	EGFR p.Leu861Gln	0	EGFR p.Gly719Ala	EGFR p.Leu861Gln	—	0
4	Sync	AC	nCT-AS-LS-aCT	EGFR p.Leu858Arg	TP53 p.Glu204*	40	EGFR p.Leu858Arg **EGFR amplification**	TP53 p.Glu204*	—	0
5	Sync	AC	nCT-AS-LS-aCT	Complete response	—	0	KRAS p.Gly12Cys	TP53 p.Arg196Gln	**TP53 p.Glu298*** **SMAD4 p.Glu337Lys** **STK11 p.Phe354Leu**	90
6	Meta	AC	LS.*AS	PTEN p.Thr167Ala	—	20	PTEN p.Thr167Ala	—	—	80
7	Meta	AC	nCT-LS-aCT*AS	MAP2K1 p.Lys57Asn	TP53 p.His193Tyr	0	MAP2K1 p.Lys57Asn	TP53 p.His193Tyr	—	0
8	Sync	AC	nCT-AS-LS-aCT	TP53 p.Gly154Val	—	20	TP53 p.Gly154Val	—	—	20
9	Sync	AC	nCT-LS-aCT-AS	KRAS p.Gly12Cys	TP53 p.His178Asp	0	KRAS p.Gly12Cys	TP53 p.His178Asp	—	0
10	Sync	AC	nCT-LS-AS	TP53 p.Val157Phe	—	0	TP53 p.Val157Phe	—	—	0
11	Sync	SCC	nCT-LS-aCT-AS	No mutation found	—	0	Not available	—	—	0
12	Meta	LCC	nCT-LS-aCT*AS	TP53 p.Tyr163Cys	—	60	TP53 p.Tyr163Cys	—	—	0
13	Meta	SCC	nCT-LS-*AS	TP53 p.Arg158Leu	—	0	TP53 p.Arg158Leu	—	—	0
14	Meta	AC	LS*AS	TP53 p.His178Metfs*68		0	TP53 p.His178Metfs*68	**BRAF p.Gly466Glu**	—	10
15	Meta	AC	LS-aCT-*AS	NA	—	0	KRAS p.Gly12Arg	—	—	0
16	Meta	AC	nCT-LS*AS	NI	—	5	TP53 p.Glu294*	—	—	0
17	Meta	LCC	RCT*AS	NA	—	0	ERBB4 p.Cys258Ser	—	—	0
18	Sync	SCC	nCT-LS.AS	No mutation found	—	0	NA	—	—	0
19	Sync	AC	RCT-AS	TP53 p.Gly266*	KRAS p.Gln25*	0	TP53 p.Gly266*	KRAS p.Gln25*	—	0
20	Sync	SCC	LS-AS	No mutation found	—	20	No mutation found	—	—	30

Differential mutations between primary and metastasis are marked in bold font.

Abbreviations: AC = adenocarcinoma; aCT = adjuvant chemotherapy; AS = adrenal surgery; LCC = large-cell lung cancer; LS = lung surgery; Meta = metachronous metastasis; NA = not available; nCT = neoadjuvant chemotherapy; NI = not interpretable; pCT = preoperative chemotherapy (before adrenal surgery); PD-L1 = programmed death-ligand 1; RCT = radio-chemotherapy; SCC = squamous cell carcinoma; Sync = synchronous metastasis; TPS = Tumor Proportion Score.

*Adrenal metastatic relapse (metachronous patients only).

Figure 1 Kaplan-Meier Plot for Overall Survival (in Months)
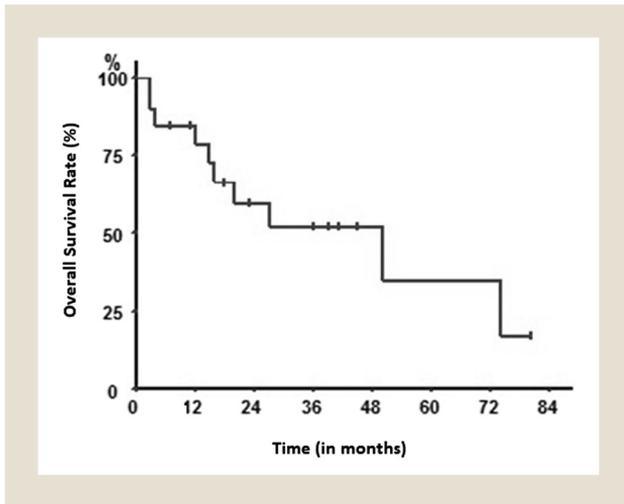
tumor cell.[20-23] Schmid carried out an analysis of molecular mutations in primary lung cancer and corresponding loco regional lymph-node metastasis and demonstrated that only 1 patient of 7 had the same *EGFR* mutation in the primary tumor and the corresponding lymph node metastasis. In the remaining 6 patients, *EGFR* mutations were identified either in the primary tumor or in the lymph node metastasis, whereas 2 patients had *KRAS* mutation in lymph node metastasis but not in the primary tumor.[24]

The implications of this finding shed an interesting light on the natural history of oligo-metastatic disease. This last one has been proposed as an evolutionary process related to the emergence of mutant clones that acquire potential for distant spread within a polyclonal population; therefore, tumor progression in oligometastatic patients might occur as the result of a limited number of mutational events, resulting a stepwise "seeding" of distant sites rather than a widespread micrometastatic dissemination in the host.[25,26] Our study confirms the possible presence of a divergent clonal evolution in metastases, although no difference in outcome was shown in patients with discordant mutations between primary and secondary tumors. However, according to the above-cited hypothesis, the use of locally ablative therapies would seem of particular interest in metastases with a divergent mutational asset from the primary tumor and should be tested in larger series.

In our series, we found that adrenalectomy, when performed in highly selected cases, may be associated with satisfactory results in terms of overall survival, with a 5-year overall survival rate of 34.5% and a median survival of 50 months. For comparison, in the above quoted pooled analysis of Gao et al,[9] the median overall survival was 18 months, and the 5-year survival rate was 28.2%.

We were not able to find factors associated with outcome, probably because of the relatively small number of patients: we only observed a trend toward worse prognosis in patients with N+ disease of the primary tumor, not reaching the significance observed by others.[9,27] Presence of lymph node metastases (N1-N2) would express the aggressive character of primitive neoplasm and its tendency to give distant spread. In agreement with previous reports,[9] we

found that histologic type had no impact on survival. We were not able to find a survival difference with respect to the synchronous or metachronous character of adrenal metastatic disease: previous works found that metachronous disease was associated with longer median overall survival than synchronous disease.[8,9,16] The reasons for explaining the longer survival of patients with metachronous metastases are still unclear: although morbidity and mortality of associated thoracic interventions could be a possible explication for shorter survival in patients with synchronous metastasis, biology of disease would be responsible for survival differences, metachronous metastasis presenting generally in the setting of less aggressive, slowly-growing cancers.[8,18]

We did not find any impact on survival of ipsilateral or contralateral character of adrenal metastasis (with respect to primary lung cancer), in agreement with the above quoted pooled analysis.[9] Thus, the question remains a matter of debate, as other reports observed a better prognosis in patients with ipsilateral metastases.[18,19] It has been hypothesized that occurrence of ipsilateral adrenal metastasis could be related to lymphatic drainage between the lung and retroperitoneum; thus it would represent a less aggressive form of regional spread, whereas in contrast, the hematogenous route, responsible of contralateral adrenal metastasis, would indicate a more aggressive disease.[28]

Surgical treatment of adrenal gland metastasis is classically performed when primary lung cancer is manageable by complete surgical resection or definitive radio–chemotherapy and in the absence of disseminated metastatic disease. However, these practices are currently evolving contemporarily with the affirmation of the concept of oligometastatic disease possible amenable to associated loco-regional treatments.[18,28,29] Treatment of metastasis in patients with oligometastatic disease may heal local disease, control symptoms, prevent complications, and possibly lengthen survival, but the impact on definitive cure is unclear: however 5-year survival rates reported by our group[13] and in previous reports[9] seem encouraging. Local treatments could help to restore the immunosurveillance; of note, an abscopal effect of radiation therapy on oligometastatic disease has been advocated.[30,31]

Our study has important limitations; in particular, owing to the small population analyzed, no definitive conclusion can be drawn about predictors of response to treatment. Furthermore, owing to heterogeneity in treatment sequence, in particular timing and duration of chemotherapy, it is difficult to allocate specific mutations at specific time points of cancer progression, because of possible selective pressure induced by treatments.

Conclusion

In conclusion, surgery may be considered an option in patients with adrenal metastasis of NSCLC, if primary tumor is controlled, and in the absence of disseminated metastatic disease. NGS may provide key elements in the future for clinical evaluation and treatment decision. Assessment of mutational patterns may provide clues on the natural history of tumor progression and provide valuable tools to identify patients with oligometastatic disease that may obtain durable benefit from locally ablative therapies.

Table 3 Overall Survival Comparisons (Log-Rank Test), With Respect to Clinical, Pathologic, and Molecular Biology Features

Feature	N (%)	P (Log-Rank Test)	5-Year Survival (95% Confidence Interval)
Gender		.93	
Male	13 (65)		29.6 (6.4-72.1)
Female	7 (35)		32.1 (6.4-76.3)
Age, y		.86	
<67	9 (45)		48.6 (19.5-78.7)
≥67	11 (55)		56.2 (27.2-81.5)
Histology		.37	
Adenocarcinoma	14 (70)		21.6 (4.6-60.9)
Non-adenocarcinoma	6 (30)		75.0 (30.1-95.4)
pT of primary lung cancer		.36	
T1-T2	15 (75)		22.1 (4.8-61.3)
T3-T4	3 (15)		100 (N/A)
Tx (no intervention)	2 (10)		100 (N/A)
pN of primary lung cancer		.59	
N0	8 (40)		68.6 (31.9-91.0)
N1	5 (25)		60.0 (23.1-88.2)
N2	5 (25)		20.0 (3.6-62.4)
Nx (no intervention)	2 (10)		100 (N/A)
Timing of metastatic disease		.43	
Synchronous	10 (50)		30.9 (6.4-74.5)
Metachronous	10 (50)		42.9 (16.9-73.4)
Site of metastatic disease with respect to primary lung cancer		.26	
Ipsilateral	11 (55)		33.7 (7.0-77.3)
Contralateral	9 (45)		38.1 (13.9-69.9)
Use of chemotherapy		.32	
Yes	16 (80)		31.4 (10.6-63.8)
No	4 (20)		66.7 (20.7-93.8)
Divergent mutational profile (n = 15)		.34	
Yes	3 (20)		75 (30.1-95.4)
No	12 (80)		25 (5.3-66.4)

Clinical Practice Points

- Management of oligometastatic (≤ 3 metastases) NSCLC integrates use of systemic and focal therapies.
- An advantage of surgical treatment is the availability of tissue to define the mutational landscape of the tumor and the presence of clonal evolution in metastases.
- Despite frequent adrenal involvement in NSCLC (20% of patients), surgical treatment of adrenal metastases is poorly reported in literature.
- Our data shows that adrenalectomy in this setting is a safe procedure correlated with 34.5% overall survival at 5 years. Most notably, mutational discordance between primary and secondary lesion was proven in 20% of patients: this information offers insight in the process of genetic diversification in metastatic disease and may provide elements for treatment decision such as correct allocation to targeted treatments.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61:69-90.
2. Walters S, Maringe C, Coleman MP, et al, ICBP Module 1 Working Group. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004−2007. *Thorax* 2013; 68:551-64.
3. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; 13:8-10.
4. Niibe Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. *Jpn J Clin Oncol* 2010; 40:107-11.
5. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small cell lung cancer: the Southwest Oncology Group experience. *J Clin Oncol* 1991; 9:1618-26.
6. Eberhardt WE, Mitchell A, Crowle J, et al, International Association for Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members, and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the M descriptors in the forthcoming eight edition of the TNM classification of lung cancer. *J Thorac Oncol* 2015; 10: 1515-22.

7. Parikh RB, Cronin AM, Kozono DE, et al. Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014; 89:880-7.

8. Tanvetyanon T, Robinson LA, Schell MJ, et al. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. *J Clin Oncol* 2008; 26:1142-7.

9. Gao XL, Zhang KW, Tang MB, Zhang KJ, Fang LN, Liu W. Pooled analysis for surgical treatment for isolated adrenal metastasis and non-small cell lung cancer. *Interact Cardiovasc Thorac Surg* 2017; 24:1-7.

10. American Cancer Society. Cancer Fact and Figures 2017. Atlanta: American Cancer Society. Avaialble at: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf. Accessed October 1, 2018.

11. David EA, Clark JM, Cooke DT, Melnikow J, Kelly K, Canter RJ. The role of thoracic surgery in the therapeutic management of metastatic non-small cell lung cancer. *J Thorac Oncol* 2017; 12:1636-45.

12. Mordant P, Arame A, De Dominicis F, et al. Which metastasis management allows long-term survival of synchronous solitary M1b non-small cell lung cancer? *Eur J Cardiothorac Surg* 2012; 41:617-22.

13. Loi M, Mazzella A, Mansuet-Lupo A, et al. Synchronous oligometastatic lung cancer deserves a dedicated management. *Ann Thorac Surg* 2019; 107:1053-9.

14. Legras A, Barritault M, Tallet A, et al. Validity of targeted next-generation sequencing in routine care for identifying clinically relevant molecular profiles in non-small-cell lung cancer: results of a 2-year experience on 1343 samples. *J Mol Diagn* 2018; 20:550-64.

15. Higashiyama M, Doi O, Kodama K, Yokouchi H, Imaoka S, Koyama H. Surgical treatment of adrenal metastasis following pulmonary resection for lung cancer: comparison of adrenalectomy with palliative therapy. *Int Surg* 1994; 79:124-9.

16. Porte HL, Roumilhac D, Graziana JP, et al. Adrenalectomy for a solitary adrenal metastasis from lung cancer. *Ann Thorac Surg* 1998; 65:331-5.

17. Mazzella A, Mastromarino MG, Zhang X, Bobbio A, Alifano M. Multimodality treatment of oligometastatic non-small cell lung cancer: review of literature. *Shanghai Chest* 2017; 1:6.

18. Howell GM, Carty SE, Armstrong MJ, et al. Outcome and prognostic factors after adrenalectomy for patients with distant adrenal metastasis. *Ann Surg Oncol* 2013; 20:3491-6.

19. Raz DJ, Lanuti M, Gaissert HC, Wright CD, Mathisen DJ, Wain JC. Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma. *Ann Thorac Surg* 2011; 92:1788-92.

20. Zhang W, Edwards A, Flemington EK, Zhang K. Significant prognostic features and patterns of somatic TP53 mutations in human cancers. *Cancer Inform* 2017; 16, 1176935117691267.

21. Zhao J, Ye X, Xu Y, et al. EGFR mutation status of paired cerebrospinal fluid and plasma samples in EGFR mutant non-small cell lung cancer with leptomeningeal metastases. *Cancer Chemother Pharmacol* 2016; 78:1305-10.

22. Frankel D, Nanni-Metellus I, Robaglia-Schlupp A, et al. Detection of EGFR, KRAS and BRAF mutations in metastatic cells from cerebrospinal fluid. *Clin Chem Lab Med* 2018; 56:748-53.

23. Li Y, Pan W, Connolly ID, et al. Tumor DNA in cerebral spinal fluid reflects clinical course in a patient with melanoma leptomeningeal brain metastases. *J Neurooncol* 2016; 128:93-100.

24. Schmid K, Oehl N, Wrba F, Pirker R, Pirker C, Filipits M. EGFR/KRAS/BRAF mutations in primary lung adenocarcinomas and corresponding locoregional lymphnode metastases. *Clin Cancer Res* 2009; 15:4554-60.

25. Correa RJ, Salama JK, Milano MT, Palma DA. Stereotactic body radiotherapy for oligometastasis: opportunities for biology to guide clinical management. *Cancer J* 2016; 22:247-56.

26. Turajlic S, Swanton C. Metastasis as an evolutionary process. *Science* 2016; 352: 169-75.

27. Collaud S, Stahel R, Inci I, et al. Survival of patients treated surgically for synchronous single-organ metastatic NSCLC and advanced pathologic TN stage. *Lung Cancer* 2012; 78:234-8.

28. Karolyi P. Do adrenal metastases from lung cancer develop by lymphogenous or hematogenous route? *J Surg Oncol* 1990; 43:154-6.

29. Zerrweck C, Caiazzo R, Clerquin B, et al. Renal origin and size are independent predictors of survival after surgery for adrenal metastasis. *Ann Surg Oncol* 2012; 19: 3621-6.

30. Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol* 2009; 10:718-26.

31. Bobbio A, Alifano M. Immune therapy of non-small cell lung cancer. The future. *Pharmacol Res* 2015; 99:217-22.