Adrenal Metastases in Lung Cancer
Clinical Implications of a Mathematical Model

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Abstract: Adrenal gland metastases are common in lung cancer. It is well recognized that aggressive treatment of solitary adrenal metastases leads to improved outcomes but the exact nature of adrenal deposits is not well understood. Controversy exists as to the routing of cancer cells to the adrenal gland with some believing that this transmission is lymphatic, in contrast to the more generally accepted theory of hematogenous spread. Recently published mathematical modeling of cancer progression strongly supports the lymphatic theory. With that in mind, we performed a literature review to look for biological plausibility of simulation results and believe that evidence supports the contention that metastases to the adrenal gland can be routed by means of lymphatic channels. This could explain improved survival for patients in whom solitary adrenal metastases are managed aggressively with surgical or radiation modalities. We are calling for clinical trials prospectively testing this hypothesis.

Key Words: Non–small-cell lung cancer, Adrenal metastasis, Lymphatogenous spread.

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For over a century, metastases have been acknowledged to be unpredictable. White[1] observed in his book *Tumors* in 1913 that "We may have a carcinoma with extensive involvement of the lymph glands and no visceral deposits, while we may find another similar carcinoma with extensive visceral tumors and no affection of the glands; or, again, we may find an extensive primary tumor without involvement of either glands or viscera." Despite advancements in medical knowledge, we have failed to quantify our understanding of metastatic progression patterns. One example is the controversy in primary lung cancer and adrenal metastases. In lung cancer, although adrenal metastases are common, there is no clear consensus as to whether they occur by means of a lymphatic or hematogenous route. Perhaps because lung anatomy does not clearly reinforce connections of lymphatics between lungs and adrenals, many would regard these metastases as primarily hematogenous. Although the lymphatic theory of adrenal gland spread is not novel as it was described by Onuigbo[2] in 1957, to date this finding is not usually acknowledged in clinical practice. A recently published Markov chain–based mathematical model of metastatic progression of primary lung cancer supports the lymphatic pathway of spread.[3,4] In this article, we briefly review the literature, discuss the new mathematical model of metastasis, and examine the strength of the evidence pointing to lymphatic connections between primary lung tumor and the adrenal gland. Proven correct, this would result in a down staging of this patient population to stage III and the related modification in treatment plan for curative intent.

MARKOV CHAIN MODEL'S CONFIRMATION OF LYMPHATIC ADRENAL SPREAD

The mathematical model,[3,4] which we refer to as the "Newton" model, uses probabilistic methods such as Markov chain dynamics, random walkers, and Monte Carlo simulations to simulate how a tumor cell moves from the primary tumor to each metastatic site. The model was generated by using an autopsy data set of 3827 untreated cancer victims.[5] For this report, we will focus on lung cancer as a primary site. The model regards metastasis-inducing cells as random walkers on an anatomic network, each anatomic site serves as a node between which cells can travel to spread disease, the autopsy data set is treated as the steady-state distribution of metastasis, and computational strategies are used to identify the route and mean first-passage times (MFPT) by which cancer cells spread to arrive at the steady state. MFPT is a quantity that tracks how many steps on average a random walker takes to reach a certain organ, starting from the primary site. The network makes no prior assumptions as to the connections between anatomic sites but uses the steady-state information (autopsy data) to infer their values. Figure 1 shows the distribution of lung cancer metastases from the original

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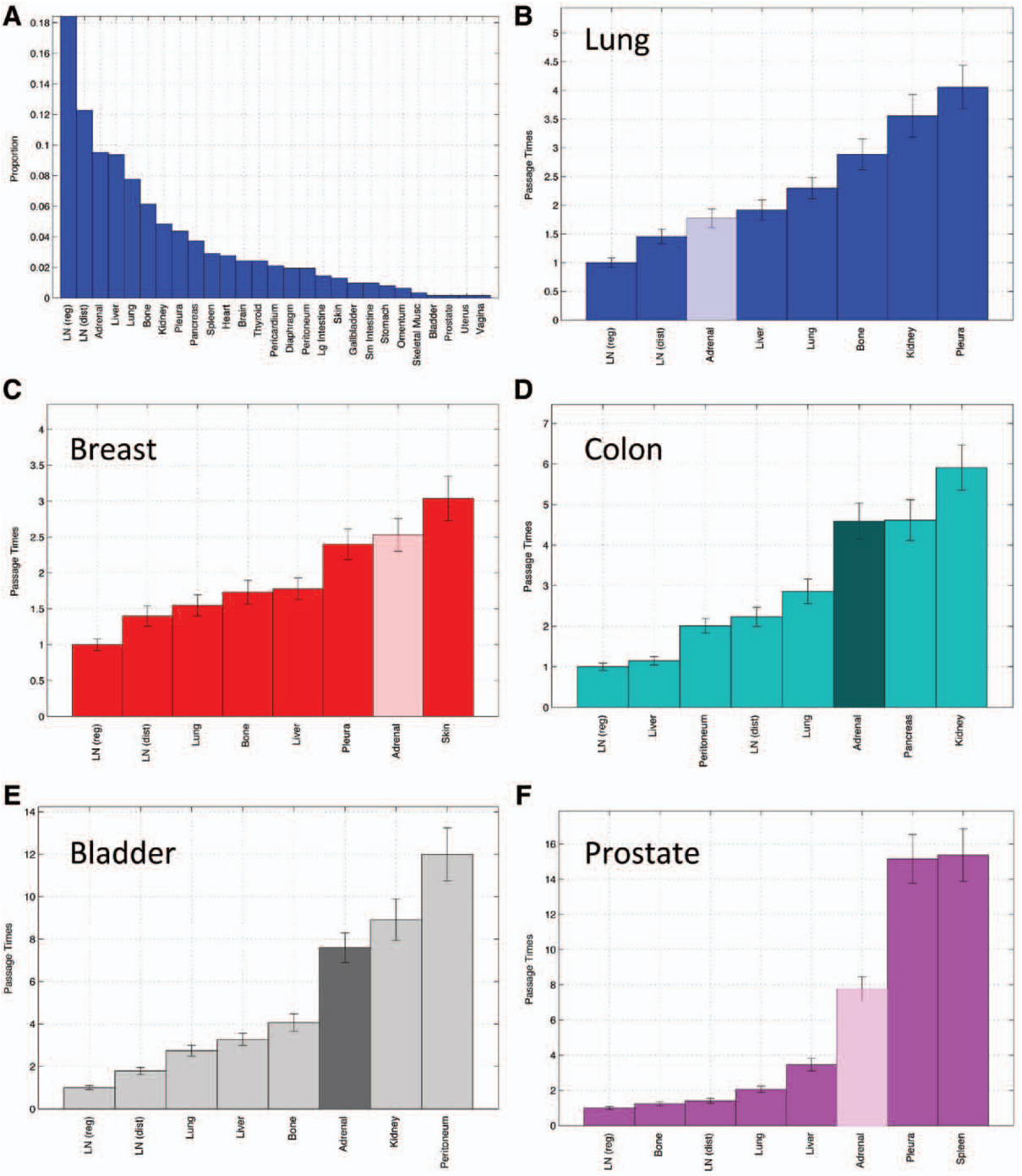

FIGURE 1. *a*, Metastatic tumor distribution for primary lung cancer from DiSibio and French data set: 163 primary lung cancer autopsies; 619 metastatic tumors; and 59 adrenal metastases. Histogram is normalized so that sum of areas is one. *b*, Mean first-passage times to other organs associated with a collection of random walkers leaving the primary lung tumor. Adrenal is the first visited site after LNs. Times are normalized so that regional LNs equal unity; others are scaled to it. *c*, Mean first-passage times to other organs associated with a collection of random walkers leaving the primary breast tumor. Adrenal is the seventh visited site. Times are normalized so that regional LNs equal unity; others are scaled to it. *d*, Mean first-passage times to other organs associated with a collection of random walkers leaving the primary colon tumor. Adrenal is the sixth visited site. Times are normalized so that regional LNs equal unity; others are scaled to it. *e*, Mean first-passage times to other organs associated with a collection of random walkers leaving the primary bladder tumor. Adrenal is the sixth visited site. Times are normalized so that regional LNs equal unity; others are scaled to it. *f*, Mean first-passage times to other organs associated with a collection of random walkers leaving the primary prostate tumor. Adrenal is the sixth visited site. Times are normalized so that regional LNs equal unity; others are scaled to it. LN, lymph node.

autopsy data set and the relative ranking of metastatic sites based on the MFPT for five primary tumors. It is clear that in lung cancer, adrenal metastases occur relatively quickly (Figure 1*b*) compared with other metastatic sites. In lung cancer, the short passage times and relatively high transition probabilities associated with adrenal metastases are in the range of what is typically seen for regional lymph node disease rather than for hematogenously spread sites. By comparison, adrenal metastasis in colon, breast, prostate, and other solid tumors (Figures 1*c–f*) do not share the short MFPT from the primary site to the adrenal.

LYMPHATIC THEORY OF ADRENAL GLAND METASTASIS IN PRIMARY LUNG CANCER

For one to accept a lymphatic theory of adrenal gland metastasis, several postulations need to be addressed. First, the presence of an anatomic connection between the primary tumor and the adrenal gland needs to be proven. Second, if those anatomic connections truly play a role in lung cancer metastasis, a preferential or earlier involvement of the adrenal gland on the ipsilateral side of the primary tumor should be seen. Lastly, patients with aggressively managed ipsilateral metastases should have improved outcomes. This is analogous to improved outcome in patients with locoregional nodal spread compared with distant metastatic disease.

Anatomic Plausibility of Direct Lymphatic Connections

From the lung, direct lymphatic tributaries exist to the thoracic duct and to celiac and para-aortic nodes.[6] This is confirmed by postmortem examination of coal miners showing coal dust deposition in retroperitoneal lymph nodes in 87% of cadavers suggesting a direct passage to the abdomen from lung.[7]

The thoracic duct is the main collecting lymphatic vessel of the chest, receiving lymphatic drainage from the abdominal viscera. The flow of lymph through the thoracic duct is unidirectionally upward due to the lymphatic vessel valvular structure and smooth muscle in the vessel wall. However, if one in theory interrupts the typical upward lymph flow, the cancer cells can potentially travel caudad and reach the adrenal gland through those connections. In examining the entire lengths of the thoracic duct postmortem, Onuigbo[8] found cancer cells in the thoracic duct in 62% of cases with the majority of cells clumping at the lymphatic valves, thus creating a potential for blockage. No human studies have looked at the flow direction in the thoracic duct in living cancer patients.

Incidence and Laterality of Adrenal Metastases in Non–Small-Cell Lung Cancer

Not surprisingly, there is an increase in the incidence of adrenal involvement as a patient's disease progresses. Clinically isolated adrenal gland metastases discovered on staging computed tomography scans in patients otherwise presumed operable are rare in the pre–positron emission tomography (PET) era and are reported in 1.6% to 3.5% of non–small-cell lung cancer.[9,10] The true number of adrenal metastases in this group is higher due to the poor ability of imaging technology to detect small tumor deposits. Matthews et al.[11] and Finke et al.[12] illustrated this point when reporting their autopsy series of patients dying within 1 month of curative lung resection. In their series, 3% to 7.6% of patients were discovered to have adrenal metastases on autopsy. Rates of adrenal involvement increase further to 9% in living metastatic cancer patients and to 25% to 39% in autopsy series.[2,13–17]

Unfortunately, laterality is rarely reported in surgical, radiation, or autopsy series. Out of 29 articles reviewed, only seven reported laterality.[2,9–36] Only five provided data sufficient to address the relevant question, and the majority of those had small numbers of patients and were retrospective. Porte et al.[18] reported higher likelihood of ipsilateral involvement, 72% versus 28% in patients with solitary adrenal metastases ($n = 43$, $p < 0.01$). Kocijancic et al.[36] reported on patients with both unilateral and bilateral adrenal metastases and noted a 50% ipsilaterality ($n = 50$). The contralateral and bilateral disease was reported in conglomerate, and thus, it is not possible to estimate the difference between ipsilateral and contralateral involvement in this study. It is important to notice that the prevalence of ipsilateral involvement depends on the total burden of metastatic disease. If adrenal is the only site of metastasis, 50% of the metastases are ipsilateral. However, if adrenal metastases are present together with other sites, the typical ipsilaterality rate is numerically lower at 25% ($p = 0.14$). In addition, if patients initially operated for stage I–IIIA disease recur in the adrenal gland, 63% of recurrences are ipsilateral compared with 37% of contralateral or bilateral. This relationship is opposite in patients presenting with nonoperable cancers (IIIB or IV) where incidence of ipsilateral disease is only 29% compared with 71% of contralateral/bilateral ones ($p = 0.034$).[36] Similar patterns are reported by Porte et al.[9] who showed that patients with ipsilateral adrenal gland involvement have lower burden of systemic disease and are less likely to have other distant metastases than if contralateral adrenal gland is involved, at 20% versus 62%, respectively.

This increased incidence of ipsilateral involvement is also confirmed in a much larger autopsy series. In patients in whom adrenal metastasis was the only metastatic site, the ipsilateral adrenal gland is 1.59 times more likely to be involved than contralateral one (61% versus 39%, $n = 405$, $p < 0.01$). In patients with more than one metastatic site, ipsilateral adrenal gland still consistently receives more metastases. This difference decreases as more metastatic sites develop and completely disappears in patients with six or more organs involved. In addition, bilateral adrenal metastases seem more common as disease progresses. For example, in a patient with four metastatic sites, the incidence of bilateral adrenal metastases is approximately 60% compared with 5% if only two metastatic sites are discovered.[17] Similar results were reported by Onuigbo[2] who examined 1000 cadavers and reported 61% prevalence of ipsilateral involvement compared with 39% contralateral. As a composite, these data indicate that as cancer progresses and hematogenous pathways become definitely involved as indicated by other distant sites of spread, the likelihood of circulating tumor cells establishing metastases in the contralateral adrenal gland increases. It is possible that

in the beginning stages of metastasis, cancer could be reaching the adrenal gland through the lymphatic channels before hematogenous metastases develop, thus explaining ipsilateral preponderance.

Differential Outcome in Aggressively Managed Ipsilateral versus Contralateral Adrenal Metastases

If managed solely with chemotherapy, even isolated adrenal metastases progress to death with reported survival of only 6 to 9 months.[10,27] No randomized clinical trials compared the survival outcome of surgically managed adrenal metastases versus chemotherapy treated ones. In a small retrospective case series by Luketich and Burt[22] (n = 14), the median survival was 31 months for patients treated with chemotherapy followed by surgical resection of both primary mass and a solitary adrenal metastasis versus 8.5 in patients treated with chemotherapy alone (p = 0.03). Reported outcomes are better with adrenalectomy and radiation therapy (16–31 mo) than medically treated metastatic disease (9–12 mo).[10,18–20,22,23,29,30,32] If involvement of the ipsilateral adrenal gland is lymphatic in origin, one should see improvement in survival if the adrenal metastasis is managed aggressively with surgery and radiation similar to an improved survival seen in patients with stage III disease compared with patients with stage IV disease. The main challenge in looking at this question is that studies reporting outcomes of aggressively managed isolated adrenal metastases fail to report outcomes based on laterality. Two studies deserve mentioning. Porte et al. in the pre-PET era showed that after resection of solitary adrenal metastases, recurrences are more common in patients with contralateral adrenal metastases than ipsilateral ones (n = 43, 83% versus 77%, $p > 0.05$). Raz et al.[27] compared survival outcomes based on the laterality of the metastasis in patients with aggressively managed adrenal metastases as defined by surgical resection together with resection of primary tumor. PET scan was not required but was performed in some patients, thus giving us a purer population in regard to undetected other distant metastases. In a small cohort of patients (n = 20), they showed improvement in 5-year survival from 0% to 83% in contralateral versus ipsilateral disease (p = 0.003).[27]

CONCLUSIONS

In summary, current models and a review of the literature suggest that there is a difference in prevalence and a possible difference in outcomes of patients with ipsilateral versus contralateral adrenal metastasis. Current guidelines such as those from the National Comprehensive Cancer Network, however, do not recommend discrimination in the treatment of adrenal metastasis based on laterality.

The last decade has seen the development of a number of improvements for the local therapy of metastatic disease, including the development of robotic assisted surgery and stereotactic radiotherapy. As these technologies reduce the burden of localized treatment of metastasis, it is critical that oncologists carefully define the populations that are most likely to benefit from interventions. Randomized, prospective clinical trials of surgical and other localized treatments will be difficult to complete in this relatively rare population. The creation of mathematical models may guide optimal anatomical sites for local therapy, but these models require clinical validation of their predictive ability. We would propose that large organizations such as the cooperative groups make an effort to create a nationwide registry of local therapy applied to oligometastatic patients. Such a registry should include surgical and radiosurgery-based approaches and could then be mined to compare the outcome with ipsilateral and contralateral treatments of adrenal tumors and answer other questions that may be relevant to the oncology community. This approach may provide the kind of prospective data that would serve both to validate existing mathematical models of metastasis and to shape guidelines for the surgical management of metastatic adrenal disease. If successful, this modeling and clinical validation strategy can be expanded to other tumor types.

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REFERENCES

1. White CP. *Tumours*. London: Constable & Co, 1913.
2. Onuigbo WI. Some observations on the spread of lung cancer in the body. *Br J Cancer* 1957;11:175–180.
3. Newton PK, Mason J, Bethel K, Bazhenova LA, Nieva J, Kuhn P. A stochastic Markov chain model to describe lung cancer growth and metastasis. *PLoS One* 2012;7:e34637.
4. Newton PK, Mason J, Bethel K, et al. Spreaders and sponges define metastasis in lung cancer: a Markov chain Monte Carlo mathematical model. *Cancer Res* 2013;73:2760–2769.
5. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. *Arch Pathol Lab Med* 2008;132:931–939.
6. Riquet M, Le Pimpec Barthes F, Souilamas R, Hidden G. Thoracic duct tributaries from intrathoracic organs. *Ann Thorac Surg* 2002;73:892–898; discussion 898–899.
7. Lawerenz JU, Baur E, Fuss U, Müller KM. [Anthracosilicosis changes in abdominal lymph nodes in miners]. *Pneumologie* 1990;44(Suppl 1):254–255.
8. Onuigbo WI. The carriage of cancer cells by the thoracic duct. *Br J Cancer* 1967;21:496–500.
9. Porte HL, Roumilhac D, Graziana JP, et al. Adrenalectomy for a solitary adrenal metastasis from lung cancer. *Ann Thorac Surg* 1998;65:331–335.
10. Ettinghausen SE, Burt ME. Prospective evaluation of unilateral adrenal masses in patients with operable non-small-cell lung cancer. *J Clin Oncol* 1991;9:1462–1466.
11. Matthews MJ, Kanhouwa S, Pickren J, Robinette D. Frequency of residual and metastatic tumor in patients undergoing curative surgical resection for lung cancer. *Cancer Chemother Rep 3* 1973;4:63–67.
12. Finke NM, Aubry MC, Tazelaar HD, et al. Autopsy results after surgery for non-small cell lung cancer. *Mayo Clin Proc* 2004;79:1409–1414.
13. Auerbach O, Garfinkel L, Parks VR. Histologic type of lung cancer in relation to smoking habits, year of diagnosis and sites of metastases. *Chest* 1975;67:382–387.
14. Galluzzi S, Payne PM. Bronchial carcinoma: a statistical study of 741 necropsies with special reference to the distribution of blood-borne metastases. *Br J Cancer* 1955;9:511–527.
15. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma; analysis of 1000 autopsied cases. *Cancer* 1950;3:74–85.
16. Bullock WK, Hirst AE Jr. Metastatic carcinoma of the adrenal. *Am J Med Sci* 1953;226:521–524.

17. Károlyi P. Do adrenal metastases from lung cancer develop by lymphogenous or hematogenous route? *J Surg Oncol* 1990;43:154–156.
18. Porte H, Siat J, Guibert B, et al. Resection of adrenal metastases from non-small cell lung cancer: a multicenter study. *Ann Thorac Surg* 2001;71:981–985.
19. 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;26:1142–1147.
20. Marangos IP, Kazaryan AM, Rosseland AR, et al. Should we use laparoscopic adrenalectomy for metastases? Scandinavian multicenter study. *J Surg Oncol* 2009;100:43–47.
21. Kim SH, Brennan MF, Russo P, Burt ME, Coit DG. The role of surgery in the treatment of clinically isolated adrenal metastasis. *Cancer* 1998;82:389–394.
22. Luketich JD, Burt ME. Does resection of adrenal metastases from non-small cell lung cancer improve survival? *Ann Thorac Surg* 1996;62:1614–1616.
23. Valeri A, Bergamini C, Tozzi F, Martellucci J, Di Costanzo F, Antonuzzo L. A multi-center study on the surgical management of metastatic disease to adrenal glands. *J Surg Oncol* 2011;103:400–405.
24. Sarela AI, Murphy I, Coit DG, Conlon KC. Metastasis to the adrenal gland: the emerging role of laparoscopic surgery. *Ann Surg Oncol* 2003;10:1191–1196.
25. Kirsch AJ, Oz MC, Stoopler M, Ginsburg M, Steinglass K. Operative management of adrenal metastases from lung carcinoma. *Urology* 1993;42:716–719.
26. Lo CY, van Heerden JA, Soreide JA, et al. Adrenalectomy for metastatic disease to the adrenal glands. *Br J Surg* 1996;83:528–531.
27. 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;92:1788–1792; discussion 1793.
28. Muth A, Persson F, Jansson S, Johanson V, Ahlman H, Wängberg B. Prognostic factors for survival after surgery for adrenal metastasis. *Eur J Surg Oncol* 2010;36:699–704.
29. Lucchi M, Dini P, Ambrogi MC, et al. Metachronous adrenal masses in resected non-small cell lung cancer patients: therapeutic implications of laparoscopic adrenalectomy. *Eur J Cardiothorac Surg* 2005;27:753–756.
30. Mercier O, Fadel E, de Perrot M, et al. Surgical treatment of solitary adrenal metastasis from non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2005;130:136–140.
31. Oshiro Y, Takeda Y, Hirano S, Ito H, Aruga T. Role of radiotherapy for local control of asymptomatic adrenal metastasis from lung cancer. *Am J Clin Oncol* 2011;34:249–253.
32. Holy R, Piroth M, Pinkawa M, Eble MJ. Stereotactic body radiation therapy (SBRT) for treatment of adrenal gland metastases from non-small cell lung cancer. *Strahlenther Onkol* 2011;187:245–251.
33. Bell JW. Abdominal exploration in one-hundred lung carcinoma suspects prior to thoracotomy. *Ann Surg* 1968;167:199–203.
34. Stenbygaard LE, Sørensen JB, Olsen JE. Metastatic pattern in adenocarcinoma of the lung. An autopsy study from a cohort of 137 consecutive patients with complete resection. *J Thorac Cardiovasc Surg* 1995;110(4 Part 1):1130–1135.
35. Sandler MA, Pearlberg JL, Madrazo BL, Gitschlag KF, Gross SC. Computed tomographic evaluation of the adrenal gland in the preoperative assessment of bronchogenic carcinoma. *Radiology* 1982;145:733–736.
36. Kocijancic I, Vidmar K, Zwitter M, Snoj M. The significance of adrenal metastases from lung carcinoma. *Eur J Surg Oncol* 2003;29:87–88.